THE AMERICAN REVIEW OF TUBERCULOSIS

OFFICIAL JOURNAL OF
THE AMERICAN TRUDEAU SOCIETY

EDITOR
MAX PINNER, New York, N. Y.

EDITORIAL BOARD

JOHN ALEXANDER, Ann Arbor, Mich.
J. BURNS AMBERSON, JR., New York, N. Y.
E. R. BALDWIN, Saranac Lake, N. Y.
H. J. CORPER, Denver, Col.
F. S. DOLLEY, Los Angeles, Calif.
BRUCE H. DOUGLAS, Detroit, Mich.
L. U. GARDNER, Saranac Lake, N. Y.
ROSS GOLDEN, New York, N. Y.
ESMOND R. LONG, Philadelphia, Pa.
LEWIS J. MOORMAN, Oklahoma City
D. W. RICHARDS, JR., New York, N. Y.

VOLUME XLVI
JULY-DECEMBER, 1942

PUBLISHED MONTHLY
AT MOUNT ROYAL AND GUILFORD AVENUES, BALTIMORE, MD.
BY THE NATIONAL TUBERCULOSIS ASSOCIATION

Medical L.b.

CONTENTS: ORIGINAL ARTICLES

NUMBER 1, JULY, 1942

The Interpretation of Haemograms in Pulmonary Tuberculosis. W. STOBIE, N. J. ENGLAND AND W. H. MCMENEMEY 1
Anaemia of Tuberculous Patients following Thoracoplasty. MORRIS M. BRAVERMAN 27
The Electrocardiogram in Pulmonary Tuberculosis. SIDNEY P. SCHWARTZ AND HENRIETTE MARCUS 35
Management of the Minimal Tuberculous Lesion. ALFRED L. KRUGER, BENJAMIN P. POTTER AND ABRAHAM E. JAFFIN 50
Pleurisy with Effusion. J. L. BONILLA, JR. 59
Ambulatory Pneumothorax. H. I. SPECTOR AND H. E. OPPENHEIMER 67
Contralateral Pneumothorax. M. LUCACER 72
Quantitative Standardization of Tuberculin Purified Protein Derivative. LAWRENCE T. CLARK AND STEPHEN F. FOLLIN 77
Tuberculin Reaction in Tuberculosis during Pregnancy. M. R. LICHTENSTEIN 89
The Effect of Pregnancy upon Experimental Tuberculosis in Rabbits. LEO J. WADE 93
A Method for Studies in Chemotherapy of Tuberculosis. W. HARRY FEINSTONE 101
Clinical and Laboratory Reports:
Spontaneous Bilateral Pneumothorax. WALTER I. WERNER AND WILLIAM H. Thearle 105
Inspection of the Lungs during Respiration. DIRAN YEGIAN 109

NUMBER 2, AUGUST, 1942

Treatment of War Wounds of the Thorax. ARTHUR H. AUFSES 111
Acute Putrid Pulmonary Abscess. ARTHUR S. W. TOUROFF AND HAROLD NEUHOF 121
Haemorrhage from the Trachea, Bronchi and Lungs of Nontuberculous Origin. CHEVALIER L. JACKSON AND SIDNEY DIAMOND 126
Treatment of Pulmonary Tuberculosis by Cadmium Sulphide. B. A. DORMER, F. J. WILES AND J. FRIEDLANDER 139
Infection, Social Environment and Heredity in Tuberculosis. GEORG WOLFF AND ANTONIO CIOCCO 142
Undiagnosed Pulmonary Tuberculosis in Elderly Persons. RAYMOND E. MILLER AND BEATRICE HENDERSON 164
Tuberculosis in Exposed Populations. HILBERT MARK 172
A Tuberculosis Case-Finding Demonstration in San José, Costa Rica. C. W. WELLS 179
Promin in Experimental Tuberculosis. WILLIAM H. FELDMAN, FRANK C. MANN AND H. CORWIN HINSHAW 187

Response of Scar Tissue to Tuberculin. DIRAN YEGIAN AND JOSEPH KURUNG 196
A New Method of Staining Tubercle Bacilli. EMIL WEISS 199
A Device for Infecting Animals by Inhalation. J. L. BLAISDELL AND A. HAMBLETON 205
Statistical Data 210
American Trudeau Society:
Report of the Committee on Industrial Tuberculosis 213

NUMBER 3, SEPTEMBER, 1942

Tuberculosis in College Students. CHARLES EVERARD LYGHT 227
Treatment of Tuberculosis with a Low Carbohydrate Diet. BENJAMIN P. SANDLER AND RUDOLPH BERKE 238
Results of Phrenic Nerve Operations. PAUL L. OWENS 262
Inhalation of Nebulized Promin in Experimental Tuberculosis. ALVAN L. BARACH, NORMAN MOLOMUT AND MAX SOROKA 268
Chemotherapy of Tuberculosis. GARY ZUCKER, MAX PINNER AND HAROLD THOMAS HYMAN 277
B-Complex Deficiency in Tuberculosis. W. H. GLASS 285
Tubercles and Foreign-Body Granulomata. WALTER PAGEL 295
Experimental Tuberculosis in Hyperglycaemic Albino Rats. M. MAXIM STEINBACH AND CHARLES J. DUCA 304
Congenital Tuberculin Hypersensitiveness and Specific Tuberculo-allergic Immunity. H. J. CORPER AND C. CLARK 309
Initial Tissue Response to Tubercle Bacilli. C. E. WOODRUFF, RUBY G. KELLY AND MARY A. LEAMING 319
Age Characteristics of Tubercles. HENRY C. SWEANY 329
Brief Notes:
Tuberculosis in a Carcinoma of the Oesophagus. DAVID T. CARR AND DAVID M. SPAIN 346
Effect of Pregnancy upon Tuberculin Reaction. RAYMOND W. CONN 350
A Portable X-ray Unit for Field Studies in Tuberculosis. JOSEPH D. ARONSON AND ROBERT M. SAYLOR 352
An Improved Steam Suction Apparatus. E. S. MARIETTE 355
Obituary—LeRoy S. Peters, 1882–1941 358
American Trudeau Society:
Report of the Committee on Coexistent Syphilis and Tuberculosis 361
Report of the Committee on Coöperation with the American Board of Internal Medicine 362

NUMBER 4, OCTOBER, 1942

The Isolation and Identification of Pathogenic Fungi from Sputum. JOSEPH M. KURUNG 365
Primary Tuberculosis. EDNA M. JONES, T. N. RAFFERTY AND H. S. WILLIS 392

The Clinical Episode in Tuberculosis and the Meteorological Environment. WILLIAM F. PETERSEN 407
Haemorrhagic-Necrotic Reaction to Tuberculin PPD. ERICH URBACH AND HAROLD L. GOLDBURGH 418
Plasma Prothrombin in Tuberculous Patients. J. W. SAVACOOL AND R. J. CHODOFF 432
Bromsulphalein Liver Function Test in Pulmonary Tuberculosis. ALFRED L. KRUGER AND ISADORE E. GERBER 439
Statistical Data 445
Books 455
American Trudeau Society:
Report of the Committee on Undergraduate Medical Education 468
Report of the Committee on X-ray Apparatus and Technique 469
Experience with Mass X-ray Equipment. HERBERT R. EDWARDS 472

NUMBER 5, NOVEMBER, 1942

Management of Patients with Occasionally Positive Sputum after Apparently Adequate Therapy:
Clinical Aspects. ARTHUR M. STOKES 475
Pathological Aspects. HENRY STUART WILLIS 479
Nursing Aspects. ESTA H. MCNETT 481
Public Health Aspects. KENNETH M. SODERSTROM 483
Medical Aspects of the Rehabilitation of the Tuberculous. LOUIS E. SILTZBACH 489
Chronic Pulmonary Tuberculosis. H. R. NAYER AND MAX PINNER 505
Bronchial Obstruction and Pulmonary Atelectasis. EDWARD M. KENT ... 524
Tuberculin Sensitivity in Children with Bone Tuberculosis. PHILIP J. HOWARD, JOSEPH A. JOHNSTON AND C. LESLIE MITCHELL 532
Hastings on Catheter Drainage of Tuberculous Cavities. JABEZ H. ELLIOTT 546
Survival of Tubercle Bacilli in Books. C. RICHARD SMITH 549
Media for Tubercle Bacilli. H. J. CORPER AND MAURICE L. COHN 560
Silicon Dioxide in Guinea Pig Inoculation for Tuberculosis. HARRIETT HOLLON, MARIAN SPRICK, ELIZABETH CONROY AND ELIZABETH WILSON 568
Clinical Notes:
Fenestration of the First Thoracic Ribs. DOUGLAS S. KELLOGG AND JOSEPH F. LINSMAN 574
Tuberculosis of the Oesophagus. ALBERT GUGGENHEIM, LOUIS ROTENBERG AND HERMAN I. LAFF 577
Editorial—The Patient with Occasionally Positive Sputum following Apparently Adequate Treatment. MAX PINNER 582
American Trudeau Society:
Report of the Committee on Tuberculosis Sanatorium Standards 584
Report of the Committee on Rehabilitation 586

NUMBER 6, DECEMBER, 1942

Studies of Mycobacteria with the Electron Microscope. MILTON B. ROSENBLATT, ERNEST F. FULLAM AND ALBERT E. GESSLER 587
Enzymes as Factors in Resistance to Tuberculosis. BRUNO GERSTL AND ROBERT TENNANT 600
Experimental Pulmonary Tuberculosis in the Dog. BCG Immunization. F. D. GUNN, J. J. SHEEHY, CHARLOTTE A. COLWELL AND M. A. MILLS .. 612
Gastric Lavage in Healthy Adolescents. C. FLOYD, H. A. NOVACK AND C. G. PAGE 622
Atypical Findings on Animal Inoculation. S. E. FRANCO AND J. GUREVITCH . 625
Pneumothorax Treatment. W. H. MORRISS 628
Ambulatory Pneumothorax. FREDERICK TICE 639
Extrapleural Pneumothorax. PAUL GEARY 646
Pneumothorax Cases Treated at a Clinic. D. R. HASTINGS AND BORGHILD BEHN 656
Treatment of Postoperative Pulmonary Complications:
From the Point of View of the Surgeon. JOHN ALEXANDER 664
From the Point of View of the Internist. H. MCLEOD RIGGINS 666
From the Point of View of the Pathologist. MAX PINNER 674
From the Point of View of the Bronchoscopist. LOUIS CLERF 675
From the Point of View of the Nurse. ALICE LOVE MANNING 676
Tuberculosis in England during War. J. B. MCDOUGALL 677
Arytenoid Extrusion with Roentgenological Studies. WILLIAM C. VOORSANGER 684
Browning's Meteoropathological Observations in Tuberculosis. WILLIAM F. PETERSEN 690
Statistical Data 697
American Trudeau Society:
Report of the Committee on Educational Literature 701
Report of the Membership Committee 703
Report of the Committee on Constitutional Revision 705

THE INTERPRETATION OF HAEMOGRAMS IN PULMONARY TUBERCULOSIS[1]

W. STOBIE, N. J. ENGLAND AND W. H. McMENEMEY

INTRODUCTION

The present investigation was undertaken in order to explore the possible value of regular examination of the blood in phthisical subjects with special reference to prognosis.

The patients concerned numbered in all 243, of whom 144 were drawn from the City of Oxford and 99 from the County of Oxfordshire. They consisted of 114 females (average age twenty-nine, youngest six, eldest fifty-nine) and 129 males (average age thirty-four, youngest eleven, eldest sixty). There were only 2 patients under the age of fifteen and there were 17 who had not attained their eighteenth birthday. In all, 947 examinations were made on these patients, but the tests were applied to many other cases not included in this series.

The controls consisted of persons admitted to the hospital on suspicion only of pulmonary tuberculosis. They were generally contacts or patients complaining of lassitude or other suspicious symptoms, who were eventually found to present no evidence of tuberculosis. Instances of nontuberculous disease of the lungs, such as bronchiectasis or new growths were excluded. These controls included 11 women (average age thirty-four, youngest sixteen, eldest fifty-one) and 7 men (average age thirty-four, youngest twenty, eldest forty-nine): they may, in our opinion, be considered a fair sample of the population and, as they have been patients under conditions identical with those which obtained for the tuberculous and have been subjected to the same haematological tests, they may be regarded as a control series.

TECHNIQUE

Times of collection: Each patient was allowed at least forty-eight hours' rest after admission before the first blood sample was taken and sometimes this was delayed till the third or fourth day.

As far as possible all bloods were collected between 10 a.m. and 12 noon. In order that results might be comparable in subsequent counts an endeavour was made to collect the samples always at the same time of the day.

Counts were made at twenty-eight day intervals in the vast majority of instances.

Blood was collected by venepuncture and all investigations made upon the same sample: a strict attention to the sharpness of the needle ensured a minimum of discomfort and therefore a minimum of psychological disturbance; the patients were in bed, except for a few of the serial counts towards the end of their stay in the hospital when they were up for a few hours daily.

Haemoglobin estimation: The Sahli-Zeiss apparatus was used, the reading being made five minutes after mixing the blood with the N/10 hydrochloric acid.

Red cell count: The usual procedure was adopted of diluting the blood 1 in 200 and counting the corpuscles in 80 of the 1/400 sq. mm. squares.

[1] From the Osler Pavilion, Radcliffe Infirmary, Oxford, England.

White cell count: The blood was diluted 1 in 20 and the cells in four of the 1 sq. mm. squares enumerated.

Blood film: Two blood films were made from each sample of blood. At first the coverslip method was preferred because of the more even distribution of cells and therefore greater degree of accuracy; but owing to the extra amount of time required in the preparation of the grease-free coverslips and their mounting, the method was abandoned in favour of the slide technique. For the same reason the differential count of 200 cells was given up in favour of one of 100 cells; it was found that, provided the films were made immediately on withdrawing the blood and dried rapidly, and given a constant "meander" technique, the 100 cell count did not differ materially from that of 200. The count was recorded on graph paper, the neutrophils, a hundred of which were reviewed, being split into five categories according to the method of Cooke and Ponder (1921). After some practice it was found possible to perform the differential and nuclear counts, with a 4 mm. objective and a thinly oiled field according to the method advocated by Evans (1938). This change introduced a considerable saving in both eye-strain and time. The differential and nuclear counts were undertaken by one of us (W. H. McM.) and by a qualified laboratory technician (R. W. D.), it having been previously determined that the agreement between both workers when the counts were estimated independently was within the error to be expected when each undertook a second count on the same sample.

Sedimentation rate: The method of Westergren was adopted: the blood was collected with a dry sterile glass syringe and introduced into a tube containing 0.4 cc. of 3.8 per cent sodium citrate and marked at the 2 cc. level. After mixing the blood the Westergren tube was filled and set up at room temperature as soon as possible after collection. A reading was taken after one hour.

GROUPING OF CASES

It was necessary to devise some system of grouping cases in order to assess the value of haemograms. The analysis was based primarily on the Ministry of Health's classification with further subdivisions into (*1*) uncomplicated effusion wherein radiological evidence of parenchymatous disease of the lung was absent and (*2*) lesions predominantly infiltrative and lacking in demonstrable excavation.

Having regard to the variations, sometimes considerable, in total and differential white counts which are found in health, it is no easy matter to attribute significance to changes met with in disease. Thus Whitby and Britton (1937) give a range of normal for the total white count from 4,000 to 10,000. What significance, therefore, is to be placed on monthly findings for total white counts of, say, 7,500, 6,000 and 10,600 in an established case of the disease? Much valuable work has been done in this connection, particularly in America, and reference will be made to these studies later, as well as those of Houghton (1935) at Colindale. What do not seem to be established with any degree of certainty are the limits of significance of changes in the blood count. Again the variations to be expected in the blood picture of pulmonary tuberculosis have been indicated but the converse has received scant attention. Thus the clinician is presented with the haemogram and may remark "just about what I expected." Should, however, the haemogram be unexpected, what attention should the clinician give to it?

STATISTICAL ANALYSIS OF HAEMOGRAMS

(a) *Initial Counts* (on admission to sanatorium) (table 1).

Control series: It will be noticed that the mean figures for the control series are within the range of normal according to Whitby and Britton.

Total white count: The case classification shows the mean readings to rise as the disease progresses (table 2A). Only 5 per cent of the control series are over the 10,000 level. This percentage however rises appreciably in the T.B. (−) and +1 categories[2] and thereafter the increment is less steep, until in the T.B. +3 group a quarter of them have a white cell count between 12,000 and 18,000.

TABLE 1

Inital count (in relation to clinical classification)

CLINICAL CLASSIFICATION	CONTROL CASES		EFFUSION		INFILTRATION		T.B. (−)		T.B. +1		T.B. +2		T.B. +3	
	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation
Total leucocytes	6,233	1,482	7,000	2,000	9,000	2,800	8,700	2,500	8,700	2,500	10,220	3,100	11,890	3,600
Neutrophil per cent	51	7	61	6	65	10	61	9	62	9	70	8	70	9
Absolute	3,060	767	4,365	1,268	6,446	2,195	5,438	1,740			7,120	2,715		
Single lobe neutrophil (per cent of neutrophils)	13	5	33	19	33	16	29	17	34	18	37	16	39	15
von Bonsdorf count	250	25	202	42	198	35	206	35	199	40	192	32	185	29
Eosinophil per cent	4	3	3	2	3	2	3	2	3	2	2	2	2	2
Lymphocyte per cent	38	6	28	7	23	9	28	9	27	7	21	7	19	7
Absolute	2,410	784	2,020	835	2,055	1,029	2,719	1,279			1,939	772		
Monocyte per cent	7	3	9	3	9	4	8	3	8	4	8	3	9	3
Absolute	413	224	612	317	676	369	806	436			776	342		
Lymphocyte monocyte ratio			4:1	2	4:1	2	4:1	2	4:1	2	3:1	2	3:1	2
Sedimentation rate (Westergren) mm. per hour	6	4	38	29	27	20	30	25	25	22	33	21	60	21
Houghton index	273	26	159	74	149	60	176	68	154	49	117	61	83	53
Total cases	15		28		48		39		17		100		75	

Neutrophils: All mean readings in the clinical groups are above that of the control mean and there is the same steady rise from "effusion" to T.B. +3 as in the case of the total white cells. But it will be noted that, whereas the percentage neutrophil count in T.B. +2 is only 70 as compared with 51 for the control, the average for the absolute count in this group is 7,120 as compared with 3,060 in the control; thus the absolute neutrophil count in this group has more than doubled itself whereas the percentage count has only risen by 50 per cent.

[2] T.B. (−); T.B. +1; T.B. +2; T.B. +3—Ministry of Health Classification for cases of pulmonary tuberculosis.

Single lobe neutrophils and Bonsdorf count: These counts both confirm the tendency towards a neutrophil leucocytosis with advancing disease, for they show a distinct shift to the left, implying an increased production of these cells.

Eosinophils and monocytes: In neither case does the mean percentage count in the T.B. classification indicate any alteration from the control. As the total white count rises with advancing disease it is obvious that the absolute figure must rise if a constant percentage count is recorded. The mean readings for the absolute monocyte count confirm this.

Lymphocytes: There are declining percentage and absolute counts as the disease advances. We find that in group T.B. +2, whereas the percentage count differs from the control by 45 per cent, the absolute count change is only 13 per cent.

Association of neutrophil and lymphocyte counts: It has already been observed that the averages for the monocyte and eosinophil percentages remain almost stationary in the clinical groupings. The other remaining components, neutrophils and lymphocytes (the basophils being too few in number to be of practical significance) appear to move in opposite directions. Reference to table 2B shows that the correlations between lymphocytes with total white cells, and neutrophils with total white cells, are nearly equal in value but opposite in sign. The correlation between lymphocytes with neutrophil cells is, however, negative and high in value. It may therefore be inferred that the association between the changes in the percentage lymphocyte and neutrophil counts is close.

It is suggested that the leucocytosis is the cause of the relative lymphopenia and inversely, an improvement in the lymphocyte percentage takes place usually because of a restitution of the neutrophil count.

Lymphocyte/monocyte ratio: The findings show that this ratio is not likely to be a useful mathematical expression. This revelation is not unexpected in view of the facts that (*a*) the averages of the monocyte counts remain almost stationary over all the clinical classifications, (*b*) the variable factor is the lymphocyte count and (*c*) the small variations which are likely to take place are concealed by division of the factor.

Sedimentation rate and Houghton index: The mean sedimentation rate is increased in all the categories of pulmonary tuberculosis, the group T.B. +3 being considerably higher than the others. It was noticed that the series of pleural effusions afforded the next highest average. A reference to table 2 shows the size of the standard deviation as a percentage of the mean and the great variation that was experienced in the records is noted. A normal sedimentation rate does not necessarily connote freedom from phthisis.

The Houghton index follows along the general trend of the sedimentation rate but reference to table 2 shows that the coefficient of variation is smaller, except in the instance of group T.B. +3.

(b) *Progress counts:* The general trend of the initial haemograms indicated that progress counts might be helpful. If marked changes in the total leucocyte or the neutrophil counts took place in association with improvement or deterioration of the patient, progress haemograms might be of considerable

value. It was unfortunate that it was not until this stage in the analysis had been reached that the desirability of absolute numbers was appreciated. As in the majority of progress haemograms only differential counts had been carried out, insufficient data on absolute figures were available to make an analysis of these possible. The final count was not included in this series.

TABLE 2

Coefficients of variation (per cent counts)

	CONTROL	T.B. −	T.B.+1	T.B. +2	T.B. +3	EFFUSION	INFILTRATION
Total leucocytes	24	29	29	30	30	29	31
Neutrophil	14	15	15	11	13	10	15
Absolute	25	32		38		29	34
Single lobe neutrophils	38	58	53	43	38	58	49
von Bonsdorf count	10	15	20	17	16	21	18
Eosinophil	75	67	67	100	100	67	67
Lymphocytes	16	32	26	33	37	25	39
Absolute	33	47		40		41	50
Monocytes	43	38	50	38	33	33	44
Absolute	54	54		44		52	55
Sedimentation rate (mm.)	67	83	88	64	35	76	74
Houghton index	10	39	32	52	64	47	40

TABLE 2A

Total white cells per cent distributions

COUNTS	CONTROL	T.B. − AND T.B. + 1	T.B. +2	T.B. +3
2,000	35.0	21.6	4.7	
6,000	60.0	49.0	47.2	33.3
10,000	5.0	29.4	36.5	37.7
14,000			9.4	24.6
18,000			2.4	4.3
Total	100.0	100.0	100.2	99.9
n	20	51	85	69

The problem was approached from the outlook of a physician, having to assess a haemogram presented to him at the bedside, that is, "is any appreciable change obvious or not?" It was argued that, if an appreciable change from the initial count was observed in the progress haemogram, and if this was associated with corresponding alterations in the patient's clinical condition on discharge, then a progress haemogram is of importance from an immediate prognostic standpoint. The difficulty was to interpret the term "appreciable change." It was

decided that a useful arbitrary limit of change would be the standard deviation applicable to each item of the haemogram relative to the appropriate clinical classification. As an example, if the average change in the progress count for a pleural effusion case was an increase of 2,000 total white cells, then this was taken to be an "appreciable change." We were advised that more complicated mathematical methods of recording the variations observed, although possible, are not practicable bedside procedures and therefore should be rejected. Table 3 shows the disappointing results. The first column of figures headed "available percentage" records the small number in which an appreciable alteration could be recorded. Other factors in the differential count showed similar results.

TABLE 2B

Correlations

Neutrophil and total white cells:	
Total	219
Neutrophil (mean)	68 ± 9
Total white (mean)	10,000 ± 3,400
C^{∞} C. = +0.30	
Lymphocytes and total white cells:	
Total	205
Lymphocytes (mean)	22 ± 9
Total white (mean)	10,000 ± 3,500
C^{∞} C. = −0.32	
Lymphocytes and neutrophils:	
Total	205
Lymphocytes (mean)	22 ± 8
Neutrophil (mean)	69 ± 9
C^{∞} C. = −0.91	

The findings were that:

1: General trends can be discerned in the table, such as improvement with a falling single lobe neutrophil count and a rising Houghton index.

2: It was felt that appreciable changes in progress haemograms should be associated consistently with corresponding variations in the clinical picture if these haemograms are to be of any clinical value. The findings demonstrate so many inconsistencies that changes in the haemogram cannot be taken for definite evidence of clinical improvement or deterioration.

3: Appreciable changes in the blood count were only recorded in about one-third of the cases under review.

(c) *Final counts:* Two methods of analysis were adopted (*1*) by grouping instances wherein "excellent" and "good" progress had been noted, and estimating the mean values of their final haemograms for comparison with their

initial blood picture or with that of their clinical group, and (*2*) by comparing the results of sanatorium treatment with the patients initial haemogram.

Table 4 shows the mean counts of 16 cases whose progress was recorded as "excellent." The total leucocytes had in point of fact increased and the only significant improvements were in the single lobe neutrophils and sedimentation rate.

TABLE 3

Progress counts

COUNT	CLASSIFICATION	AVAILABLE	RISING BY σ					FALLING BY σ				
			Group	Improved	Stationary	Worse	Died	Group	Improved	Stationary	Worse	Died
		per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
Total neutrophil	Effusion	35	21	14			7	14	14			
	Infiltration	44	16	16				28	16	4	8	
	T.B. −	15	5	5				10	10			
	T.B. +2	11	7	3		4		4	2		2	
Monocyte per cent	Effusion	70	35	28	7			70	35			7
	Infiltration	36	20	12	8			16	4	12		
	T.B. −	30	10	10				20	20			
	T.B. +2	17	8	4	2	2		9	6	2	1	

σ = Standard Deviation.

TABLE 4

Mean counts of 16 cases whose progress was excellent

	PRIMARY COUNT	SECOND COUNT	FINAL COUNT
Total white cells	10,400	12,200	11,300
Neutrophils	67%	65%	64%
Single lobe neutrophils	31%	22%	17%
von Bonsdorf count	201	224	230
Lymphocytes	23%	23%	26%
Monocytes	8%	8%	8%
Sedimentation rate (mm.)	30	14	14

The T.B. group +2 was selected for the analysis of "good" progress counts (table 4A) as this furnished 32 patients. Here the single lobe neutrophil was the only item in the haemogram that could be utilized for demonstration of improvement. All other changes were too small to be of practical use when the normal variations associated with haemogram technique were taken into consideration. Table 4B shows a further random sample taken from the "infiltration" group and, in this, patients were divided into two classes according to whether they had improved or deteriorated, those who underwent special forms

of treatment being excluded. This series shows that the haemogram did not demonstrate the clinical progress and in the majority no significant change in the blood picture took place; and that where material changes were recorded they were not always those which one might have anticipated on the basis of existing theories, for example, the monocyte count showed variations both rising and falling whether the patient improved or got worse.

Table 5 records a sample of the endeavour to relate the patient's progress while in sanatorium with the initial haemogram. The vertical columns record clinical progress and are divided into two main broad groups, those whose counts were either above or below that of the mean value of the clinical group under

TABLE 4A

Mean values of final counts of 32 cases T.B. +2 whose progress was considered to be good

		T.B. +2 MEAN PRIMARY COUNT
Neutrophils	66%	70%
Single lobe neutrophils	24	37%
von Bonsdorf count	220	192
Lymphocytes	25%	21%
Monocytes	7%	8%

TABLE 4B

Infiltrations—not treated by sanocrysin or pneumothorax

Difference between initial and final counts

	6 CASES WHO DID WELL			6 CASES WHO DID BADLY		
	Down by σ	Up by σ	No change	Down by σ	Up by σ	No change
Single lobe neutrophils			6			6
Total neutrophils	3	1	3	1		5
von Bonsdorf count	1		5	2		4
Lymphocytes	1	1	5		1	5
Monocytes	1	1	2	1	1	4

σ = Standard Deviation.

analysis. The horizontal columns record the various items of the haemogram each with a subdivision into two groups, those whose counts approximated to the mean and those who differed to the extent of the standard deviation, as recorded in table 1. The figures indicate that it does not seem possible to attach any prognostic significance to high or low readings of the primary haemogram when dealing with any individual case, the errors in interpretation being too high.

(d) *Indices:* Indices were worked out from the independent data already amassed and they were plotted on scatter charts (charts 1, 2 and 3), firstly against each other and secondly each against the sedimentation rate. The

results show a satisfactory correlation between the Frimodt-Möller and Barton, and Houghton indices, and from it one can imply that, as the former is the easier to perform, it is for this reason the index of choice. The correlation, however, between each of the indices and the sedimentation rate is not close, substantiating the findings of many authors, including Houghton, that this test does not parallel and is not as reliable as an index. It would seem, however, that the sedimentation rate carries rather more weight in the Frimodt-Möller and Barton index than in the other.

TABLE 5

Single lobe neutrophil cells

CLASSIFICATION	WITH COUNTS ABOVE MEAN READING OF GROUP RESULT OF TREATMENT							WITH COUNTS BELOW MEAN READING OF GROUP RESULT OF TREATMENT					
		Total of group	Per cent of group	Improved	Stationary	Worse	Died		Per cent of group	Improved	Stationary	Worse	Died
				per cent	*per cent*	*per cent*	*per cent*			*per cent*	*per cent*	*per cent*	*per cent*
Effusions	Above mean	14	36	29			7	Below mean	64	57	7		
	Above mean + S.D.		21	14			7	Below mean − S.D.	28	21	7		
Infiltrations	Above mean	25	64	36	12	4		Below mean	36	20	12	4	
	Above mean + S.D.		24	12		12		Below mean − S.D.	16	16			
T.B. (−)	Above mean	19	31	26		5		Below mean	68	47		16	5
	Above mean + S.D.		21	16		5		Below mean − S.D.	5	5			
T.B. +2	Above mean	84	49	24	11	14		Below mean	51	32	7	11	1
	Above mean + S.D.		18	7	4	7		Below mean − S.D.	19	15	2	1	1
Total		142											

S.D. = Standard Deviation.

(e) *Treatment* (*artificial pneumothorax*): Houghton has recorded some graphs which appeared convincing as to the value of haemograms in recording the progress of pneumothorax cases. Our own experience is not so happy. Table 6 has been prepared in a similar way to table 4B, except that the sorting has been into 3 groups according to the clinical result. A total of 47 cases, all taken from group T.B. +2 have been selected. The improved cases only recorded a definite change in the haemogram, and this in only one-third of the examples. An error of about 10 per cent is recorded. For those deteriorating, the results are still less constant, while, for those classed as stationary, the haemogram recorded a number of definite changes, up to 50 per cent showing improvement!

ANAEMIA IN PULMONARY TUBERCULOSIS

At the outset of this study it was resolved to undertake a haemoglobin estimation and a red cell count on each patient within four days of admission to hospital. The results are shown in table 7. The total number of cases was

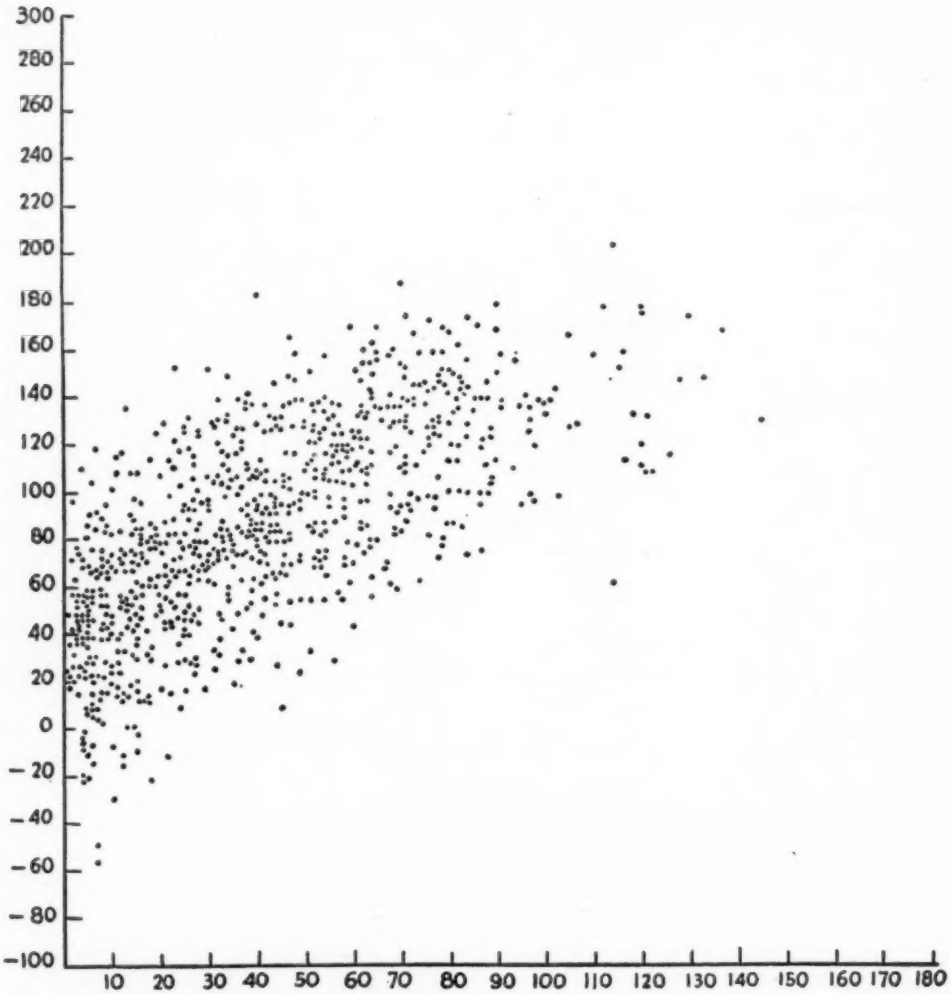


CHART 1. Sedimentation rate = abscissae. Frimodt-Möller and Barton index = ordinates

377 which is a small series on which to base conclusions. Nevertheless, certain trends are not without interest and if the findings could be substantiated for a much larger series of cases, they may be of significance. The patients were chosen so that other pathological conditions, and especially coexisting diseases causing anaemia, such as carcinoma of the bronchus, haemorrhoids and duodenal ulcer, could be excluded with a reasonable degree of certainty.

In the first place, it is shown (as far as the 85 per cent haemoglobin level is concerned) that the haemoglobin of women tends to be lower than that of men. However if the 75 per cent and 70 per cent levels be studied it will be seen that in women the incidence of anaemia is highest between the ages of fifteen and twenty, next between twenty and twenty-five and finally round about the time

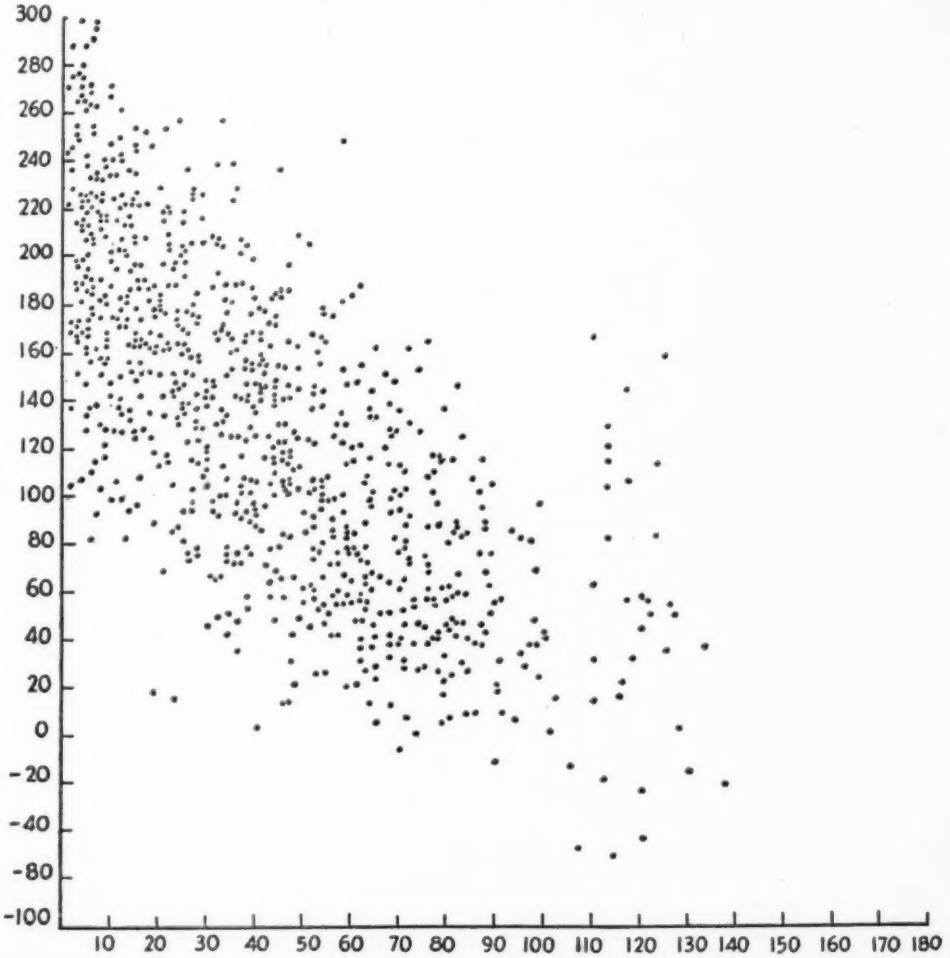


CHART 2. Sedimentation rate = abscissae. Houghton index = ordinates

of the menopause forty to fifty-five, although the number of cases in the critical age period of forty-five to fifty is regrettably small. In males, on the other hand, the ages of fifteen and twenty appear to be singularly free of any degree of anaemia, but with advancing years there is a tendency towards anaemia with a maximum between the ages of forty-five to sixty. This incidence of anaemia shows a certain parallelism with the mortality curve of pulmonary tuberculosis,

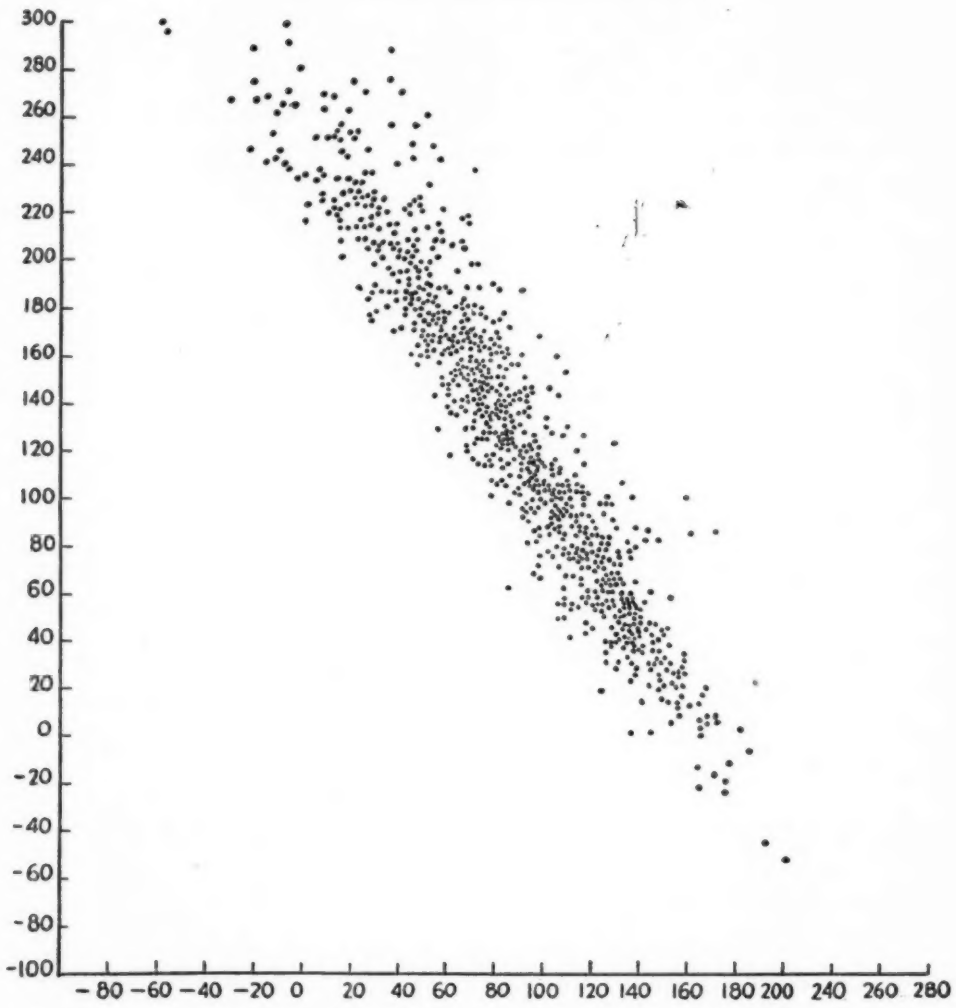


CHART 3. Frimodt-Möller and Barton index = abscissae. Houghton index = ordinates

TABLE 6

Pneumothorax cases—(T.B. +2)

	IMPROVED: 29 CASES			STATIONARY: 10 CASES			WORSENED: 8 CASES		
	Down by σ	Up by σ	No change	Down by σ	Up by σ	No change	Down by σ	Up by σ	No change
Single lobe neutrophil.....	10		19	5	1	4	1		7
Total neutrophil.....	9	3	17	3		7	2	2	4
von Bonsdorf count.....	1	12	16	1	5	4			8
Lymphocytes.....	2	11	16		3	7	1	2	5
Monocytes.....	7	4	18	2	1	7	2	1	5

σ = Standard Deviation.

although with a notable exception in women in their mid-thirties, but the number of deaths in this particular series was too few for any parallelism to be noted between the incidence of anaemia and the death rate. Several of the more anaemic patients, especially the adolescent girls, were not noted for a particularly severe form of the disease, while a perusal of the blood counts of those who died did not discern any undue tendency to anaemia. The impression gained was that the anaemic element was not necessarily a feature of the severe form of the disease but a large scale investigation would be needed to establish this presumption as a fact. The subject is not only of academic importance for, if it could be shown that a nation-wide policy directed towards the correction of anaemic tendencies in adolescent women counteracted the present retardation in decline in respiratory tuberculosis mortality at this age (D'Arcy Hart and Payling Wright, 1939), a decrease in morbidity rate might also be anticipated. While

TABLE 7

	AGE GROUPS								
	15–20	21–25	26–30	31–35	36–40	41–45	46–50	51–55	56–60
Men									
Number of patients.....	18	27	37	39	29	15	21	5	12
Haemoglobin under 85%....	11%	11%	16%	11%	14%	27%	47%	40%	33%
Haemoglobin under 80%....	0	11%	11%	8%	10%	0	29%	20%	0
Haemoglobin under 75%....	0	8%	5%	8%	10%	0	23%	20%	0
Haemoglobin under 70%....	0	0	2%	2%	7%	0	5%	20%	0
Women									
Number of patients.....	31	36	30	22	23	17	6	9	0
Haemoglobin under 85%....	48%	38%	37%	27%	43%	47%	33%	57%	0
Haemoglobin under 80%....	35%	25%	13%	9%	21%	23%	17%	33%	0
Haemoglobin under 75%....	22%	17%	3%	5%	0	6%	0	11%	0
Haemoglobin under 70%....	19%	3%	3%	5%	0	6%	0	11%	0

anaemia could not be regarded as an essential factor in the general causation of tuberculosis because its occurrence is not constant over the whole field of age groups, yet in so far as it would appear to be most marked at times of life when the mortality from tuberculosis is high (with the one exception of third decade females), it may still prove to be a primary factor associated with the high mortality at these ages. Three possible reasons for the association of anaemia and pulmonary tuberculosis in adolescent women call for investigation. (*1*) Is this a time of life when nutritional anaemia is common ("lipstick before butter") and therefore when, possibly for this reason or because of concomitant manifestations of malnutrition, susceptibility to pulmonary tuberculosis is high? On the face of it this is a likely explanation but Shiskin and Gloyne (1938) found that there was no appreciable difference between normal rabbits and those rendered anaemic when they were experimentally infected with tuberculosis. (*2*) In adolescence, there is a possible strain on the haemopoietic

activities of the bone marrow because of the rapid period of growth and sexual maturation. If the subject is in a state of chronic subnutrition, perhaps with relative iron starvation, is this when the tuberculous toxin may be expected to show its maximum destructive action in the marrow? (*3*) Some endocrinological factor possibly enhances the tuberculous disease process and this may account for the well known incidence of phthisis in women during the sexual period of life. Lay authors have noted a supposed increase of fertility in the tuberculous, while empirically codliver oil has stood the test of time as a therapeutic agent. Presumptive evidence would seem to justify an enquiry into sterol metabolism in this disease.

Another point of interest is the association in this series of anaemia and tuberculosis in women between forty and fifty-five. This calls for investigation. Just before the menopause chronic microcytic anaemia is common. Yet it is exceptional to meet with this disease, or with pernicious anaemia, in association with phthisis. The factors which produce chronic microcytic anaemia—frequent child bearing and lactation, menorrhagia, poverty and malnutrition, leading in turn to lack of energy and loss of appetite—would appear to be ideal for the development of phthisis. But chronic microcytic anaemia improves spontaneously after the menopause and is, in fact, unusual after this age, whereas, in the present series, anaemia associated with tuberculosis shows a peak in the quinquennial group subsequent to the menopause.

As this anaemic tendency is noticeable in both middle aged men and women with pulmonary tuberculosis, it behooves us to consider for a moment the fact that a not inconsiderable percentage of instances of carcinoma of the bronchus have a positive sputum (Maxwell and Nicholson, 1930). How far can it be said that anaemia has any influence in the development of tuberculosis or carcinoma or both in persons of this age group?

The not infrequent finding of carcinoma of the upper digestive tract in persons with chronic microcytic anaemia may be a parallel instance. The association of these two is more than fortuitous and the degenerative changes in the mucosa which may accompany or even precede the development of the anaemia, and which predispose to a cancerous change, have been interpreted as a collateral and indirect manifestation of malnutrition. A similar mechanism is conceivable in this instance.

Cruikshank (1940) has recently discussed the topography of the relative distribution of cancer and tuberculosis and considers that the subject is worth exploring. On the other hand, Hamilton and Wexler (1940) are impressed with the rarity of the association of phthisis and pulmonary carcinoma and speak of those who believe that the one condition predisposes to the development of the other as being in a minority. Evidently work is required on this subject.

We repeat that no deductions can be drawn from so small a series but the evidence to date suggests that a carefully planned statistical analysis of anaemia in this disease is called for.

Conclusions: Our findings suggest the desirability of estimating the haemoglobin in cases of tuberculosis and actively treating any below the normal level

especially in women round about puberty and the menopause. They suggest also a careful scrutiny at these ages for tuberculosis when women present themselves with the symptoms of anaemia.

DISCUSSION

Kayne, Pagel and O'Shaughnessy (1939) remark that the fundamental principle underlying the present fashion of assessment of prognosis in phthisis by a study of the leucocyte is the assumption that the cells in the blood are an exact mirror of those in the lesion. While in general there is a parallel between cytological changes in the peripheral blood stream and in the vicinity of the pathological lesion, there are in bacterial diseases many exceptions to it: a patient with lobar pneumonia may weather the course of the illness, with a total leucocyte count within normal limits, and a large cerebral abscess may present a neutrophil count abnormal only in regard to nuclear pattern. It seems reasonable therefore to expect such exceptions in phthisis. Apart from this consideration, one must visualize the phthisical lung as being composed of numerous lesions of varying ages and stages of repair so that the reflection in the peripheral blood stream cannot be more than an average of them all, an average which is liable to be disturbed by any minor exacerbation of the disease associated with the formation of new tubercles. Houghton (1935) has taken note of this situation but finds that such minor recrudescences do not notably alter the blood picture.

A survey of contemporary literature on haemograms reveals a divergence of opinion concerning their merit; also there are many differences in technique and accepted standards of normality, with a suggestion of an inherent bias in favour of either the bed-side or the laboratory methods of study. There are technical reasons for these divergent views which merit attention. They will be mentioned in the course of the discussion of our results in relation to those of others. An excellent review on the whole subject of haemograms in pulmonary tuberculosis has recently been published by Adelman (1939).

The methods of analysis carried out in our series were designed to test not so much the general trend of blood pictures, as these have been aptly analyzed, but the validity of individual counts and their variations, for one is naturally inclined to place more weight on wide variations in the blood count than on small movements. The results have been given in the summary of each section but it is felt desirable to epitomize one's findings of the basic concepts of the leucocyte reaction.

Total leucocyte and neutrophil count: We find that, as the disease advances, the leucocyte count tends to rise; this rise is due to an absolute neutrophil leucocytosis. This finding agrees with that of Holmes (1897), Medlar (1929), Kelley (1934), Boissevain, Forster and Good (1936) and Elwood and De Cecio (1939). Medlar states that an increase of neutrophils over the normal spells caseation, and that the total leucocyte count roughly reflects the volume of deranged tissue with which the leucocytes have to cope. He qualifies this remark, however, by saying that the extent or location of the tuberculous process cannot be told by the leucocyte reaction for a case of incipient tuberculosis may show as ab-

normal a leucocyte count as one in which the disease is far advanced. He regards the normal differential count for neutrophils as lying between 50 and 64 and the total leucocyte as from 6,000 to 9,000. Kelley's (1934) conclusions are similar. He recognizes a leucocyte count of 9,000 or over, consisting of more than 6,000 neutrophils and less than 2,000 lymphocytes, as a septic type of count indicative of ulceration. Elwood and de Cecio (1939) speak of elevated total leucocytic and neutrophilic counts as being significant of an exudative or a cavernous lesion or both. They say that with the development of the disease there is a slight tendency to a neutrophil leucocytosis and that the application of this knowledge to the initial clinical estimation of tuberculosis conceivably merits consideration. Frimodt-Möller and Barton (1933) have a lower standard of normal for the neutrophil percentage, namely, 45 to 55, but this may well be attributed, in part at any rate, to climatical reasons. They state that the height of a neutrophil percentage may be of prognostic value, but only if it is considered in relation to the stage of the disease. We found however that, although there was the general trend towards a neutrophil leucocytosis, it did not of necessity indicate that the patient was seriously or mildly ill or had a good reaction. A leucocytosis may occur in a simple pleural effusion or because of dental sepsis or some other complicating disease. Moreover the extent or the leucocytosis for any individual patient did not appear to be related consistently to their progress while in the hospital, nor was it necessarily related to the extent of the disease. We have to consider first the variations in accepted standards of normality and second to allow for the fluctuations in the count which may be normal for any particular person. Most workers seem to have been aware of the latter fallacy and more detailed reference will be made to it later. With regard to the accepted standards of normality for the total white count as we have previously remarked, Whitby and Brittain (1937) accept any figure between 4,000 and 10,000. In the calculation of Crawford's leucocyte index, however, figures below 6,000 and over 10,000 are regarded as prejudicial to the patient and accordingly the index is loaded, two points for every 1,000 cells above 10,000 to 13,000 and three points are added per thousand above this figure while four points for every 1,000 cells below 6,000 to 4,000 and six points per thousand below this (Medlar, 1935). The possible importance of total numbers as against percentage figures was realized early in our study, but time did not permit of its employment in the progress counts. Kelley (1934) remarked that absolute numbers are probably more reliable than percentages but Bandelier and Roepke (1913) say that more information can generally be obtained from a stained blood preparation than from the more tedious blood counts. Houghton (1934) found stained films alone sufficiently reliable.

Variations in the normal neutrophil percentage may well have their origin in differences of technique employed by the several workers. There are many important observations on this score which are of moment and deserve recall. Some workers are content with a simple technique, whereas others employ time-consuming and laborious methods. Wiseman and Doan (1934) stress the need "for exquisite technical precision" if haemograms are to be of any value. It

behooves us to ascertain how necessary this is and what degree of precision is required for such observations to be of value.

First, a simple but important experiment carried out by Heaf (1936) must be mentioned. Blood was taken from a freely flowing stab wound in the ear in 3 cases, 2 tuberculous patients and one normal person. The films were then sent to eleven competent authorities who were asked to do a differential count on each of the three slides. The figures varied as follows:

	1st case	*2nd case*	*3rd case*
Neutrophils	38.0–72.0%	59.0–76.5%	30.5–51.0%
Eosinophils	1.0– 5.0%	7.0–15.3%	1.0– 4.5%
Lymphocytes	12.0–29.5%	4.0–19.0%	36.0–65.0%
Monocytes	4.5–40.0%	4.0–16.0%	2.0–15.0%

These alarming variations may have been in part due to the fact that eleven separate films were made from each case and they could not be made from the same drop of blood, neither could they be made at the same instant, while the abnormally high monocyte percentage met with in case 1 may have been due to "ear monocytosis," a phenomenon mentioned by Schilling (1929). He and others noticed that a monocytosis may occur in healthy or slightly ill individuals when the first drop of blood is used without preliminary rubbing of the ear. Schilling believes it to represent an infarct of the circulation monocytes in the cool and stagnating vessels of the ear. Such considerations however do not dispel the likelihood of variations accruing to differences in methods of counting. When a single film made from a venepuncture was sent round to the same pathologists, the variations were as follows:

Neutrophils	63.3–75.0%
Lymphocytes	0.5– 3.2%
Eosinophils	20.6–30.0%
Monocytes	4.0–10.0%

These differences are therefore due to individual technique employed by the various pathologists. Heaf maintains that the stab method is unreliable and, if comparable results are to be obtained, the blood must be obtained by venepuncture. This question, however, has been carefully studied by MacGregor, Richards and Loh (1940), who conclude that the extent of discrepancy between finger (and the same applies to ear) and vein blood counts depends not so much upon variations in the count as variations arising from failure to obtain an adequate flow of capillary blood or to maintain a sufficiently thorough mixture of the venous blood after removal. Provided it is collected satisfactorily, there should be little difference between finger and venous blood. With this view we are in entire agreement. It is imperative that the film be made as soon as possible after the blood is drawn, and the operation of spreading and drying the films should be as speedily executed as is possible. In our view, the possibility of the "ear monocytosis" phenomenon, which may not be as rare as is believed, should be sufficient deterrent to preclude the use of the ear for the collection of

capillary blood for this purpose, even if the ear is well rubbed up and the first drop discarded.

Of the methods of spreading the blood, the coverslip technique is favoured by Boveri (1938) who considers it more accurate than the slide method for the enumeration of lymphocytes (each technique having been compared with a direct lymphocyte count in a Buerker chamber); he considers the normal to be 20 to 30. He recommends, however, the more convenient slide technique for hospital use, it being wiser to sacrifice precision to uniformity; by this method he regards a normal lymphocyte count as from 25 to 40. *Prima facie*, the coverslip technique should give a more accurate result because it entails less trauma and passive movement of the cells while the drying process is quicker. MacGregor, Richards and Loh (1940) believe that the coverslip method can be expected to give a lymphocyte count lower than normal and practically equivalent with that obtained by counting a slide film along its straight edge. They believe that the most accurate count is to be got by the "battlement edge" method of a slide. The "straight edge," "battlement edge" and "cross sectional" methods were shown to give in the same film a variation which exceeded 20 per cent. The practical issue of these experiences, therefore, is that any technique is satisfactory provided it is standardized in the one hospital and that the technical procedure a patient goes through should be identical on subsequent haematological examinations.

If a sedimentation rate is being done it is obviously to the patient's advantage that the total leucocyte count and films should be prepared at the same time with the blood withdrawn by venepuncture. It is important that the syringe and needle should be dry, that pressure on the vein cephalic to the point of puncture should be minimal and of as short a duration as is compatible with efficiency, and that, as the blood is being transferred from the syringe to the vessel, the needle should be removed and the blood pushed out gently into the latter. If the slide technique is being used some form of "spreader" is desirable, while with both slide and coverslip techniques perfectly grease-free glass is essential.

With regard to the number of cells in the differential count, Barnett (1933) advocates 300. Kaminsky (1933) 200, Houghton (1935) 200, Medlar (1936) 400, Morriss and Wilson (1936) 200 to 400. We have always made a practice of counting 100 cells as a routine, and a second hundred in abnormal cases, and have been impressed with the close association which obtains as between the 100 and 200 counts provided a "battlement edge" or "cross sectional" technique is maintained. Accordingly, it was decided at the outset of this study that time would only suffice for a 100 count, although several were, at various times throughout the investigation, given the benefit of a 200 count. Moreover it was argued that if the accuracy of the haematological investigation necessitated long and tiring differential counts, the financial and other implications would prohibit its use as a routine. Goldner and Mann (1938) have described the statistical errors accruing to differential counts.

An important consideration is the time of day and the physiological state of the patient. It is generally agreed that serial blood counts should be done at

the same time of the day, while there are many observations as to the importance of the physiological state of the patient.

Jacobsen (1926) has noted a difference in the total leucocyte count according to whether the patient is standing up or lying down; while Garvey and Butler (1929) recommended overnight fasting and one hour's complete rest before a count.

Adelman (1939) used basal conditions in a side room and studied the difference in cases of bone tuberculosis when the samples were taken during rest and activity. The mean range of total leucocyte count showed no significant variation between basal and active states, the coefficient of variation being 6.5 per cent and 8.5 per cent, respectively. During activity only one exceeded known inherent limits of error with ± 18.9 per cent out of 150 counts. He failed to note any post-prandial leucocytes or rhythm. As between rest and exercise, however, there was a slight relative and absolute increase of neutrophils at the expense of the lymphocytes, the mean leucocytic index for basal cases being 14.7 as against 16.7 for activity, but in only one individual out of 15 was variation in mean leucocytic index so great as to transfer it from "sl" unfavourable to "v" unfavourable. Medlar (1929), however, observed total leucocytic variations between 2,000 and 4,000, whether in bed or at work. Kaminsky (1933) found increases following brief mild activity of 200 or over in 40 per cent of his patients and differences in differential counts amounting to over 100 per cent. He therefore recommends that blood counts should be done under basal conditions, although Medlar (1936) found that, while leucocyte indices were higher during activity, the shift did not alter to an appreciable extent the pathological interpretation of the leucocyte picture, and he concludes that the normal variations in the leucocyte picture do not invalidate the use of the leucocyte count in interpreting pathological processes in which the leucocytes participate.

Nuclear count: Intimately associated with the raised neutrophil count is the shift to the left of the neutrophils. The nuclear patterns in tuberculosis were studied by Arneth (1905) and by Stephani-Cherbuliez (1928). In 1929 Bredeck made use of the Schilling modification of the nuclear count, applying it in conjunction with the subcutaneous tuberculin test; he concluded (1933) that together they are our most delicate and accurate method in the diagnosis of early manifestations of the disease and induced focal activity.

Ramel (1932) regarded a shift to the left as being more accurate than the sedimentation rate. Houghton (1934) employed the von Bonsdorf figure (von Bonsdorf, 1913) (that is, the weighted mean of the nuclei multiplied by 100) which necessitates the execution of a Cooke and Ponder (1921) modification of the Arneth nuclear count. The normal von Bonsdorf figure, Houghton regards as 275, a value in keeping with the usual accepted Cooke and Ponder standard. Many authors however make use of a simpler form of the nuclear count. Frimodt-Möller and Barton (1933) find the ordinary Schilling haemogram sufficient regarding the average *stabkernige* count as being 7.8 and Paine and Austin (1937) make use of the filament non-filament count introduced by Farley, St. Clair and Reisinger (1930). Kelley regarded a rise of non-filamentous neutro-

phils exceeding 16 per cent of the total neutrophils, or 960, as nearly always indicating a septic process. Mullin and Large (1931) regard the normal non-filamentous percentage as being on the average 12.6 per cent and varying from 8 to 16 per cent, counting 100 cells in 15 controls. They say that the slide method is entirely unsatisfactory. Paine and Austin (1937) counted 200 cells and found the normal varied from 2 to 16 per cent with an average of 7.7 per cent. Farley, St. Clair and Reisinger, in 190 normal persons, found 8 per cent of non-filamentous cells on the average with a maximum of 16 per cent. An important point is raised by Young (1935) who states that, if attention is paid only to the percentage and not to the absolute figures, a shift to the left may occur in the absence of infection; according to this author, this can happen either because of reduced output of polymorphonuclears without delay in removal, or by earlier removal, with or without a normal output.

Eosinophils: Holmes (1897) noted that these cells tended to disappear when the disease advanced. We found a tendency in this direction, the percentage eosinophil count falling slightly with advancement of the disease. Müller and Brösamlen (1922) and Piney (1932) consider the eosinophil to be of prognostic significance, while the latter author (1928) comments on a very well marked eosinophilia which may develop after injection of tuberculin. In our experience the variations met with are too great to justify paying any attention to this count.

Lymphocytes: It has been stated by many observers that a patient with a good lymphocyte count is likely to do well. This has been maintained by Ullom and Craig (1905), Webb and Williams (1909), Solis, Cohen and Strickler (1911), Watkins (1911), Webb (1912), Murphy and Ellis (1914) and Murphy and Sturm (1919). The difficulty is to determine what is a "good lymphocyte count." Shaw (1927) gives the normal percentage as 22.6 to 51.2 per cent, Medlar (1929) as 25 to 39 with a total minimum of 2,000. Wiseman and Doan (1934) speak of a prognostic shift in the case of these cells. Smithburn, Sabin and Hummell (1937) followed the course of the disease in rabbits and found that the lymphocyte is more reliable than the monocyte for prognosis, for the degree of decline is roughly proportional to the severity of the infection. Turley and Dougherty (1940) demonstrated a lymphocytosis in guinea pigs inoculated with tubercle bacilli but these counts were higher than any in human disease. When the lymphocytes exceed 30 per cent, there is a tendency, according to Medlar, to heal. Kurung (1935) found normal lymphocyte counts in those who had clinically healed.

It would seem, however, that a lymphocyte percentage is on the average low when the disease is active, merely because the neurophil percentage is raised. The lymphocyte percentage tends to be restored to normal figures by the decline in the neutrophil leucocytosis as the patient gets better.

Monocytes: The tendency towards a monocytosis in tuberculosis was noted by Holmes (1897) and by Lacapère (1902). Its importance has been stressed by Cunningham, Sabin, Sugiyama and Kindwall (1925), Sabin, Doan and Cunningham (1926), Morriss and Tan (1927), Cunningham and Tompkins (1928),

Blackfan and Diamond (1929), Flinn (1929), and Finner (1930). The first of these authors demonstrated the significance of the M/L ratio. Medlar (1929) regards the normal monocyte percentage as lying between 6 and 9 with an absolute maximum of 700. Over this figure there is an implication of new tubercle formation. With this view Kelley (1924) does not agree, while Bredeck (1929) holds that a high monocyte count may indicate a good outlook. Oatway (1930) says that a monocytosis adds to the danger of the septic count. While in general we believe this statement to hold true, our findings are in agreement with those of Elwood and De Cecio (1937), who find that no particular significance can be attached to the monocyte count. Neither do we find the M/L ratio to be significant nor a satisfactory mathematical expression. Nevertheless Sabin, Doan and Forkner (1930) claim the M/L ratio to be more important than either the lymphocyte or monocyte counts themselves, while Smithburn, Sabin and Hummell (1937) find the M/L ratio to be a more sensitive indicator of tuberculosis in experimental animals than any of the other blood cells alone.

Sedimentation rate: Many observers regard this as the most accurate laboratory mirror of the stage of activity of the disease (Kelley, 1936, Robins, 1937). Houghton (1934), however, has drawn attention to many fallacies in connection with this test when it alone is studied in phthisis, and for this reason advocates the use of an index. Spector and Muether (1932) find the nuclear count more useful than the sedimentation rate.

Our findings are in keeping with those of Kelley and of Robins, namely that the sedimentation rate is the most constantly altered feature of the haemogram; nevertheless it is frequently unreliable and the coefficient of variation touches 80 per cent. It may be quite normal in a case of early haemoptysis where clinical and radiological evidence of the disease is present. On the other hand, both it and the nuclear count may be altered by reason of dental sepsis. Alterations in the haemogram are noted by Kelley in severe colds, gastro-intestinal and pelvic disorders, while Nathan (1938) warns against possible fallacies occasioned by menstruation. Kayne, Pagel and O'Shaughnessy (1939) say that complications and superimposed infections must be ruled out before a haemogram can be accepted, but they find that colds and mild bronchitis do not alter the differential count although they may modify the sedimentation rate. Houghton (1934) speaks of "a bronchitic picture" with a relatively high von Bonsdorf count and a raised seimentation rate. He says that such a picture, in the absence of apparent bronchitis, may be expected to fare badly with artificial pneumothorax, thoracoplasties and permanent phrenicolysis.

The techniques in use are legion but the original method of Westergren (1921) is probably the most constantly employed and there seems no good reason for abandoning it in favour of any alternative technique. It, however, is no more than a relative test, being of value in following the progress of an illness from week to week, although there is a well defined range of normality which is of use in diagnostic work. The refinement introduced by Day (1940) in the reading of this test merits attention although it is more laborious.

Indices: The various indices were introduced in order to furnish a composite

picture. It was not intended, however, that they should detract from the value of each independent item of the haemogram. Thus Crawford (1935) and Medlar (1935) both urged that, the degree of pathological activity having been determined by the index, the components of the formula be studied in order to get a complete understanding of the phase of the tuberculosis process with which we are dealing. Behr, however, (quoted by Kayne, Pagel and O'Shaughnessy) found the Crawford index to be fallacious in 50 per cent of cases. This index, however, makes no use of the sedimentation rate. Masten (1937) recommends using both because of individual variations in each.

The indices of Frimodt-Möller and Barton (1933) and of Houghton (1934) go further than that of Crawford for they incorporate the sedimentation rate. They are therefore of more importance.

Frequency and value of haemograms: The claim for the value of serial counts appears to lie in the fact that, because of the wide range of normality, one might give an unduly pessimistic or optimistic prognosis if attention was paid to one reading only. Nevertheless, Kelley (1934) regards any one count as being sufficiently reliable for the basis of an opinion. The other reason for the advocacy of regular counts is the possibility of anticipating a relapse. Frimodt-Möller and Barton (1933), Kaminsky (1935) and Elwood and De Cecio (1937) all notice instances in which serial counts were or could have been of value in anticipating events. But in order to do this they would have to be done at fairly frequent intervals, say weekly or even twice weekly. Most workers seem to have recorded their observations monthly, but Boissevain, Forster and Good performed them every six months only. Medlar states that it is not possible to tell by the blood count when the disease is healed. Medlar and Pesquera (1931), Deegan (1934) and Houghton (1934) find the haemogram useful in following the process of collapse therapy, pleural effusion not materially altering the picture. Houghton (1934) also speaks of the value of haemograms in following the progress of out-patients, while Friedman, Dameshek and Hawes (1932) speak of its value in the diagnosis as well as the prognosis of hilar lymphadenitis. Griesbach (1930) tells of the need for a "serial prosecution of the haemograms" in order to establish an accurate prognosis. Morriss and Wilson (1936) found agreement between the haemograms and the clinical picture in 75 per cent and say that the haemogram is of use if interpreted with correct understanding of its limitations. Elwood and De Cecio (1939) remark "a wide test of the validity of a more detailed concept of the significance of leucocyte changes found a concurrence with established standards in 61 per cent of several hundred instances of pathological changes." They conclude "the broad application of concepts advanced for the interpretation of leucocyte counts however scientifically sound, finds insufficient clinical correlation . . . our results and conclusions support the seldom reported, but not uncommon opinion of the clinical inadequacy and not infrequent fallibility of the white blood cell picture."

Our findings are in agreement with the last expression of opinion and it would appear that, although the sedimentation rate has a compliance with the clinical disease in the majority of instances, the additional information given by the

laborious serial leucocyte counts does not justify their performance as a routine. The changes which take place as a result of tuberculous disease produce alterations in the blood picture which in our judgment cannot be related to the clinical condition in a large number of instances. As it is impossible to tell whether the case under review is one whose blood picture is or is not a fair reflection of the clinical condition, it must be assumed that in such cases an optimistic or pessimistic view may be engendered quite unjustifiably by reference to the differential count.

The other view is that of Duffey (1932) who, while recognizing limitations of laboratory methods, makes a plea for using all approaches to the study of the disease, since none of them is infallible. His remarks were directed primarily to the question of diagnosis but the view can well be advanced in a consideration of day to day prognosis.

When there is a question of disagreement between the clinical and haemotological picture, Medlar regards the latter as being the more accurate always. Elwood and De Cecio (1939) take the opposite view, being impressed with the accuracy of a combined clinical and radiological judgment as against a differential leucocyte count.

Kayne, Pagel and O'Shaughnessy (1939) summarize the value of haemograms in this way: "a normal picture may be useful in confirming that a lesion is non-progressive or healed. Repeated counts may be of assistance in indicating regression and healing of a lesion under treatment and in detecting relapses in the stage of inconspicuous symptoms."

Our findings suggest that little reliance can be placed on haemograms if it is desired to estimate the extent and follow the process of the disease on paper. Such findings, however, do not countenance complete abandonment of this particular laboratory method. To our way of thinking, although it may be of interest to follow the course of the disease with blood counts, it can be of no real assistance, and at the best can only confirm a clinical judgment. It is possible, however, that haemograms might be better employed in the healing case when the time has come for the patient to get about. Weekly counts at this stage of the disease may possibly be of value and merit consideration.

SUMMARY

1. The records of 243 patients have been analyzed in order to correlate their haemograms with their clinical condition and progress while in the sanatorium.

2. The results are recorded in each section dealing with a particular item of the haemogram and relative to the period of the patient's stay in the sanatorium.

3. These findings are also compared with the results of other workers in the discussion.

4. Briefly the findings are:

(*a*) The most outstanding feature in the haemogram is the leucocytosis and shift to the left that takes place in pulmonary tuberculosis. On the average this increases as the disease advances and frequently some restoration towards normal takes place as the patient gets better. However there are so many

exceptions to this rule that the degree of leucocytosis cannot be taken to indicate the extent, seriousness, or activity of the disease in any individual patient.

(*b*) In this series no absolute lymphocytosis was demonstrated in any one of the patients. It was shown that the percentage of the lymphocyte count was in most instances determined largely by the size of the neutrophil percentage.

(*c*) It was not found that any other factor of the count was constantly affected by the tuberculous process.

(*d*) Neither was it found that any factor in the count could be relied upon to assess the changes in or progress of the patient and therefore that it most certainly could not be used in any way for immediate or long term prognosis.

(*e*) A secondary anaemia was demonstrated in several cases. Its greater incidence in young adults and middle age suggests that it may be an important factor in causation and therefore worthy of further study.

SUMARIO

1. Analízanse las historias de 243 enfermos a fin de correlacionar sus hemogramas con el estado clínico y evolución durante su estancia en el sanatorio.

2. En cada sección dedicada a un punto dado del hemograma se consignan los resultados, relacionándolos con el período de permanencia del enfermo en el sanatorio.

3. Compáranse estos hallazgos con los resultados de otros investigadores.

4. Sucintamente, los hallazgos son éstos:

(*a*) La característica más notable del hemograma es la leucocitosis y desviación a la izquierda que tiene lugar en la tuberculosis pulmonar. En conjunto, esta desviación se acentúa a medida que avanza el mal, y frecuentemente obsérvase alguna evolución hacia la normalidad a medida que el enfermo mejora. No obstante, hay tantas excepciones a esta regla que no puede tomarse la intensidad de la leucocitosis como signo que indique la extensión, gravedad o actividad de la dolencia en ningún enfermo dado.

(*b*) En esta serie no se observó linfocitosis absoluta en ninguno de los enfermos, quedando demostrado que el porcentaje de la fórmula linfocitaria era determinado en gran parte, en la mayoría de los casos, por el porcentaje de neutrófilos.

(*c*) No se observó ningún otro factor de la fórmula que fuera afectado constantemente por el proceso tuberculoso.

(*d*) Tampoco se demostró que cupiera atenerse a ningún otro factor de la fórmula para justipreciar las alteraciones de la evolución del enfermo, y por lo tanto, que pudiera emplearse en modo alguno para el diagnóstico inmediato o tardío.

(*e*) En varios casos se observó una anemia secundaria, indicando su mayor frecuencia en los adultos jóvenes y personas de edad mediana que tal vez sea un factor importante en la etiología, y por lo tanto, acreedor a estudios ulteriores.

We wish to express our thanks to Professor R. A. Fisher, Dr. Bradford Hill, Dr. E. B. Ford and Dr. R. Gloyne for their advice and criticism in the preparation of this paper and to Mr. R. W. Deacon of the Osler Pavilion for his technical assistance and helpful co-operation.

BIBLIOGRAPHY

(1) Adelman, M. H.: Am. Rev. Tuberc., 1939, *39*, 70.
(2) Arneth, J.: Die Lungenschwindsucht, Leipzig, 1905.
(3) Bandelier, B., and Roepke, O.: A Clinical System of Tuberculosis, 1913, p. 344.
(4) Barnett, C. W.: J. Clin. Investigation, 1933, *12*, 77.
(5) Blackfan, K. D., and Diamond, L. K.: Am. J. Dis. Child., 1929, *37*, 233.
(6) Boissevain, C. H., Forster, A. M., and Good, B. D.: Am. Rev. Tuberc., 1936, *34*, 477.
(7) Bonsdorff, A. von: Beitr. z. Klin. d. Tuberk., 1913, Supp. Bd. 5, 1.
(8) Boveri, R. M.: Guy's Hosp. Rep., 1938, *89*, 112.
(9) Bredeck, J. F.: Amer. Rev. Tuberc., 1929, *20*, 52; 1933, *27*, 377.
(10) Cooke, W. E., and Ponder, E.: The Polynuclear Count, 1921.
(11) Crawford, A. M.: Am. Rev. Tuberc., 1935, *31*, 611.
(12) Cummins, S. L.: Tubercle, 1931, *12*, 155.
(13) Cunningham, R. S., Sabin, F. R., Susiyama S., and Kindwall, J. A.: Bull. Johns Hopkins Hosp., 1925, *37*, 231.
(14) Cunningham, R. S., and Tompkins, E. H.: Am. Rev. Tuberc., 1928, *17*, 204.
(15) Day, G.: Lancet. 1940, *1*, 1160.
(16) Deegan, J. K.: Am. Rev. Tuberc., 1934, *30*, 256.
(17) Duffy, J.: Tubercle, 1932–33, *14*, 60, 113.
(18) Elwood, B. J., and DeCecio, T.: Am. Rev. Tuberc., 1939, *39*, 641.
(19) Evans, F. L.: J. Lab. & Clin. Med., 1938, *23*, 646.
(20) Farley, D. L., St. Clair, H., and Reisinger, J. A.: Am. J. M. Sc., 1930, *180*, 336.
(21) Finner, L. L.: Am. Rev. Tuberc., 1930, *21*, 764.
(22) Flinn, J. W.: Ann. Int. Med., 1929, *2*, 622.
(23) Friedman, E., Dameshek, W., and Hawes, J. B.: Am. Rev. Tuberc., 1932, *25*, 24.
(24) Frimodt-Möller, C., and Barton, R. N.: Tubercle, 1933, *14*, 529.
(25) Garrey, W. E., and Butler, V.: Am. J. Physiol., 1929, *90*, 355.
(26) Goldner, F. M., and Mann, W. N.: Guy's Hosp. Rep., 1938, *88*, 54.
(27) Griesbach, R.: Ztschr. f. Tuberk., 1930, *56*, 177.
(28) Hamilton, C. E., and Nathan, H. W.: Am. Rev. Tuberc., 1940, *42*, 334.
(29) Hart D'Arcy and Wright, G. P.: Tuberculosis and Social Conditions in England with special reference to young adults, N. A. P. T., 1939.
(30) Heaf, F.: Lancet, 1936, *1*, 1142.
(31) Holmes, A. M.: J. A. M. A., 1897, *29*, 828.
(32) Houghton, L. E.: Tubercle, 1935, *17*, 49.
(33) Houghton, L. E.: Brit. M. J., 1936, *2*, 1246.
(34) Jacobsen, E.: Hospitalstid, 1926, *69*, 197.
(35) Kaminsky, J.: Am. J. M. Sc., 1933, *186*, 484.
(36) Kaminsky, J.: Am. Rev. Tuberc., 1935, *31*, 480.
(37) Kayne, G. G., Pagel, W., and O'Shaughnessy, L.: Pulmonary Tuberculosis, 1939.
(38) Kelley, W. O.: Bull. Johns Hopkins Hosp., 1934, *55*, 171.
(39) Kurung, J. M.: Am. Rev. Tuberc., 1935, *31*, 217.
(40) Lacapère, G.: Thèse de Paris, 1902, *20*, 18, quoted by Smithburn.
(41) MacGregor, R. G. S., Richards, W., and Loh, G. L.: J. Path. & Bact., 1940, *51*, 337.
(42) Masten, A. R.: Am. Rev. Tuberc., 1937, *36*, 239.
(43) Maxwell, J., and Nicholson, W. A.: Quart, J. Med., 1930, *24*, 29.
(44) Medlar, E. M.: Am. Rev. Tuberc., 1929, *20*, 312; 1935, *31*, 621, 642.
(45) Medlar, E. M.: Arch. Int. Med., 1936, *57*, 367.
(46) Medlar, E. M., and Pesquera, G. S.: Am. Rev. Tuberc., 1931, *23*, 367.
(47) Morriss, W. H., and Tan, S. H.: Ibid., 1927, *16*, 729.
(48) Morriss, W. H., and Wilson, G. C.: Ibid., 1936, *33*, 66.
(49) Müller, O., and Brösamlen, O.: Beitr. z. Klin. d. Tuberk., 1922, *50*, 289.

(50) Mullin, W. V., and Large, G. E.: J. A. M. A., 1931, *97*, 1113.
(51) Murphy, J. B., and Ellis, A. W.: J. Exper. Med., 1914, *20*, 397.
(52) Murphy, J. B., and Sturm, E.: Ibid., 1919, *29*, 1.
(53) Nathan, N. J. S.: Brit. J. Tuberc., 1938, *32*, 104.
(54) Oatway, W. H.: Am. Rev. Tuberc., 1930, *21*, 786; 1934, *29*, 73.
(55) Paine, D., and Austin, K.: Ibid., 1937, *35*, 221.
(56) Piney, A.: Diseases of the Blood, 1st ed., 1928, p. 155; 2nd ed., 1932, p. 249.
(57) Ramel, F.: Beitr. z. Klin d. Tuberk., 1932, *80*, 374.
(58) Robins, A. B.: Am. Rev. Tuberc., 1937, *35*, 763.
(59) Sabin, F. R., Doan, C. A., and Cunningham, R. S.: Tr. Nat. Tuberc. A., 1926, *22*, 252.
(60) Sabin, F. R., Doan, C. A., and Forkner, C. E.: J. Exper. Med., 1930, Supp. No. 3.
(61) Schilling, V.: The Blood Picture, London, 1929, p. 203.
(62) Shaw, A. F. B.: J. Path. & Bact., 1927, *30*, 1.
(63) Shiskin, C., and Gloyne, S. R.: Am. Rev. Tuberc., 1938, *38*, 325.
(64) Smithburn, K. C., Sabin, F. R., and Hummell, L. E.: Ibid., 1937, *36*, 673.
(65) Solis-Cohen, M., and Strickler, A.: Boston Med. & Surg. J., 1911, *165*, 563.
(66) Solis-Cohen, M., and Strickler, A.: Am. J. M. Sc., 1911, *142*, 691.
(67) Spector, H. I., and Muether, R. O.: Am. Rev. Tuberc., 1932, *25*, 533.
(68) Stephani-Cherbuliez, G., and Adamo, R.: Riv. di. pat. e clin d. tuberc., 1932, *6*, 794.
(69) Turley, L. A., and Dougherty, T. F.: J. Lab. & Clin. Med., 1940, *25*, 828.
(70) Ullom, J. T., and Craig, F. A.: Am. J. M. Sc., 1905, *130*, 386.
(71) Watkins, W. W.: J. A. M. A., 1911, *57*, 2129.
(72) Webb, G. B.: Bull. Johns Hopkins Hosp., 1912, *23*, 231.
(73) Webb, G. B., and Williams, W. W.: Colorado Med., 1909, *6*, quoted by Adelman.
(74) Westergren, A.: Brit. J. Tuberc., 1921, *15*, 72.
(75) Whitby, L. E. H., and Britton, C. J. C.: Disorders of the Blood, 3rd ed., 1939.
(76) Wiseman, B. K., and Doan, C. A.: Am. Rev. Tuberc., 1934, *30*, 33.
(77) Young, C. J.: Brit. M. J., 1935, *2*, 109

ANAEMIA OF TUBERCULOUS PATIENTS FOLLOWING THORACOPLASTY

MORRIS M. BRAVERMAN[1]

Anaemia is often observed in patients with pulmonary tuberculosis. The frequency of this associated anaemia (1) is 46 per cent of all admissions to a large tuberculosis sanatorium. The frequency and severity of anaemia are variable and are influenced by the characteristics of the clinical course of the pulmonary lesion. Bed-rest with or without some type of collapse therapy usually helps to control the anaemia. In some cases this must be supplemented by an adequate course of iron therapy and various dietary measures.

Nevertheless, anaemic patients frequently approach their stages of operation inadequately prepared by anti-anaemia therapy. The anaemia, then, becomes more pronounced during thoracoplasty, particularly with third and fourth stages. This report is based on the study and treatment of the anaemia existing in tuberculous patients prior to and because of thoracoplasty.

MATERIAL

One hundred and forty-three patients were observed in this study; 54 came from Middlesex County Sanatorium, Waltham, Massachusetts and 89 from William H. Maybury Sanatorium and Herman Kiefer Hospital in Northville and Detroit, Michigan. The experiment was carried on from April, 1934 to the end of June, 1941. The study was not continuous, but all patients were sufficiently observed during their operative course.

All but one were diagnosed pulmonary tuberculosis and all had thoracoplasty. The diagnosis of tuberculosis was confirmed in 142 by the repeated finding of tubercle bacilli in the sputum. The other had tuberculous empyema, proved bacteriologically. Roentgenograms of the chest were taken routinely.

Ages ranged from thirteen to fifty-five years and the average age was thirty-two. There were 82 males, or 57.3 per cent. The patients were further classified according to the National Tuberculosis Association into moderately advanced pulmonary tuberculosis, 19, or 13.2 per cent, and far advanced, 124, or 86.7 per cent. Of the complications affecting red blood corpuscle and haemoglobin in pulmonary tuberculosis, tuberculous empyema, intestinal tuberculosis and tertiary lues are most common.

METHODS

The operations were done at the Peter Bent Brigham Hospital, Boston and Herman Kiefer Hospital, Detroit. Beginning in April, 1934 and through June, 1941 the resident surgical staff of both institutions made their blood studies independently of the author. For the most part they were not requested or required to report or treat any of the patients specifically for anaemia. The surgical residents ordered blood counts before and after stages of thoracoplasty and treated the cases according to their own inclination. The interns and laboratory technicians did single red blood corpuscle and haemoglobin determinations on capillary blood. These counts were made on all patients admitted to the surgical services and were occasionally repeated.

[1] 9219 Dexter Blvd., Detroit, Michigan.

To supplement the single counts, duplicate determinations for greater accuracy were made by the author on 93 patients and on venous specimens.

From June, 1939 through June, 1941, 49 operated patients were treated specifically for their anaemia. Such treatment will be discussed below.

A sample of venous blood was taken from the cubital vein. Five cc. were withdrawn without stasis, collected and mixed in small bottles containing 0.05 cc. of a 20 per cent potassium oxalate solution. Whenever duplicate determinations were made, the pipettes and counting chamber used were certified by the U. S. Bureau of Standards.

Rib resection material was obtained at thoracoplasty practically simultaneously with venous blood specimens. In many instances this was repeated at each stage of thoracoplasty. This bone marrow material from the ribs, together with smears of the peripheral blood, will become the basis of a later correlative study and report.

Wintrobe haematocrit tubes were used in the determination of the sedimentation index and haematocrit percentage of the red blood corpuscles.

For a more detailed description of laboratory methods and normal values used in this study the reader is referred to a previous publication (1).

CLINICAL OBSERVATIONS

Before undertaking thoracoplasty, it is desirable that pulmonary tuberculosis come under some measure of control as determined by clinical and X-ray studies. Consequently, the associated anaemia often disappears. Bed-rest and adequate diet are important anti-anaemia factors. However, there still remains a group of patients who have either slight or border-line anaemia at the time of their first stage operation. Those patients, whose red blood corpuscle and haemoglobin levels are at or close to the minimum of the range of normal, are classified in the "border-line" group of anaemia. Practically all patients, if not treated specifically and adequately before and throughout their operative course, develop an increasing anaemia with each stage of thoracoplasty. The anaemia becomes most marked with third and fourth stages. By this time the untreated anaemic patient has the usual "washed-out, pallid" appearance.

The red blood corpuscles with their haemoglobin can be considered as circulating respiratory assistants. Increasing postoperative anaemia, in the face of a decreasing respiratory bed, following stages of thoracoplasty, becomes an important handicap to a proper oxygenation of tissues. Postoperative recovery may be delayed. Fortunately, all the patients are on strict bed-rest and the demands upon respiration and metabolism are minimized.

The frequency of anaemia in 94 tuberculous thoracoplasty patients for each stage of operation is recorded in table 1. Border-line anaemia patients are included in this table because they readily become anaemic under stress. Operative interference is obviously accompanied by an increase in the incidence of anaemia. A more complete account illustrating the effects of the stages of thoracoplasty upon the blood picture in tuberculous patients is outlined in table 2.

A gradually increasing microcytic hypochromic anaemia appears invariably with each stage of operation. Columns marked M.C.V. (mean corpuscular volume of the red blood corpuscle or the average red cell size) and M.C.H.C.

(mean corpuscular haemoglobin concentration or average distribution of haemoglobin mass among the cells) bear out this contention. The mean corpuscular haemoglobin of the red blood corpuscle tends to remain at or near the lower limits of normal. The normal range for mean corpuscular haemoglobin is between 33 and 38.

The effects of a fourth stage of thoracoplasty upon the blood picture are usually a little more marked in red cell and haemoglobin drop than that which occurs with a third stage. Usually the interval between a fourth or fifth or sixth or

TABLE 1

The incidence of anaemia for each stage of operation in the treatment of pulmonary tuberculosis by thoracoplasty

STAGE	NUMBER OF CASES	ACTUAL ANAEMIA	BORDERLINE ANAEMIA
First	94	28 (30%)	16 (17%)
Second	55	35 (64%)	14 (25%)
Third	21	14 (67%)	4 (19%)

TABLE 2

Haemogram to show the results of the stages of thoracoplasty in tuberculous patients

STAGE	RBC	Hgb		WBC	S.I.	VOL. PER CENT	MCV	MCHC	NUMBER OF PATIENTS
		per cent	*grams*						
Males									
First	4.6	81.8	12.8	9.1	31.8	38.1	84.9	35.2	56
Second	4.2	74.4	11.6	9.0	26.2	35.0	75.7	34.0	34
Third	4.2	73.9	11.5	9.5	15.5	32.7	71.0	37.3	11
Females									
First	4.7	83.5	13.0	10.4	30.1	40.0	90.1	32.3	40
Second	4.0	74.3	11.6	9.7	39.2	33.4	82.8	33.9	23
Third	4.1	71.5	11.1	7.7	33.8	32.0	78.1	34.1	10

S.I. = sedimentation index. MCV = mean corpuscular volume. MCHC = mean corpuscular haemoglobin concentration.

seventh stage of operation is so long that the patient has had sufficient time for proper haematopoiesis.

In some cases a drop in the white blood cell count and in the sedimentation index of the red blood corpuscles occurs before the third stage of thoracoplasty. The sedimentation index (S.I.) during an operative course is usually an unreliable indicator of the effectiveness of thoracoplasty. Often it becomes more elevated because of the absorption of tissue products from the operative wound and from the immediate effects of collapse therapy upon tuberculous disease.

Table 2 further reveals that, even though the red cell count and size and the haemoglobin all decrease, still the amount of haemoglobin distributed through-

To supplement the single counts, duplicate determinations for greater accuracy were made by the author on 93 patients and on venous specimens.

From June, 1939 through June, 1941, 49 operated patients were treated specifically for their anaemia. Such treatment will be discussed below.

A sample of venous blood was taken from the cubital vein. Five cc. were withdrawn without stasis, collected and mixed in small bottles containing 0.05 cc. of a 20 per cent potassium oxalate solution. Whenever duplicate determinations were made, the pipettes and counting chamber used were certified by the U. S. Bureau of Standards.

Rib resection material was obtained at thoracoplasty practically simultaneously with venous blood specimens. In many instances this was repeated at each stage of thoracoplasty. This bone marrow material from the ribs, together with smears of the peripheral blood, will become the basis of a later correlative study and report.

Wintrobe haematocrit tubes were used in the determination of the sedimentation index and haematocrit percentage of the red blood corpuscles.

For a more detailed description of laboratory methods and normal values used in this study the reader is referred to a previous publication (1).

CLINICAL OBSERVATIONS

Before undertaking thoracoplasty, it is desirable that pulmonary tuberculosis come under some measure of control as determined by clinical and X-ray studies. Consequently, the associated anaemia often disappears. Bed-rest and adequate diet are important anti-anaemia factors. However, there still remains a group of patients who have either slight or border-line anaemia at the time of their first stage operation. Those patients, whose red blood corpuscle and haemoglobin levels are at or close to the minimum of the range of normal, are classified in the "border-line" group of anaemia. Practically all patients, if not treated specifically and adequately before and throughout their operative course, develop an increasing anaemia with each stage of thoracoplasty. The anaemia becomes most marked with third and fourth stages. By this time the untreated anaemic patient has the usual "washed-out, pallid" appearance.

The red blood corpuscles with their haemoglobin can be considered as circulating respiratory assistants. Increasing postoperative anaemia, in the face of a decreasing respiratory bed, following stages of thoracoplasty, becomes an important handicap to a proper oxygenation of tissues. Postoperative recovery may be delayed. Fortunately, all the patients are on strict bed-rest and the demands upon respiration and metabolism are minimized.

The frequency of anaemia in 94 tuberculous thoracoplasty patients for each stage of operation is recorded in table 1. Border-line anaemia patients are included in this table because they readily become anaemic under stress. Operative interference is obviously accompanied by an increase in the incidence of anaemia. A more complete account illustrating the effects of the stages of thoracoplasty upon the blood picture in tuberculous patients is outlined in table 2.

A gradually increasing microcytic hypochromic anaemia appears invariably with each stage of operation. Columns marked M.C.V. (mean corpuscular volume of the red blood corpuscle or the average red cell size) and M.C.H.C.

(mean corpuscular haemoglobin concentration or average distribution of haemoglobin mass among the cells) bear out this contention. The mean corpuscular haemoglobin of the red blood corpuscle tends to remain at or near the lower limits of normal. The normal range for mean corpuscular haemoglobin is between 33 and 38.

The effects of a fourth stage of thoracoplasty upon the blood picture are usually a little more marked in red cell and haemoglobin drop than that which occurs with a third stage. Usually the interval between a fourth or fifth or sixth or

TABLE 1

The incidence of anaemia for each stage of operation in the treatment of pulmonary tuberculosis by thoracoplasty

STAGE	NUMBER OF CASES	ACTUAL ANAEMIA	BORDERLINE ANAEMIA
First	94	28 (30%)	16 (17%)
Second	55	35 (64%)	14 (25%)
Third	21	14 (67%)	4 (19%)

TABLE 2

Haemogram to show the results of the stages of thoracoplasty in tuberculous patients

STAGE	RBC	Hgb		WBC	S.I.	VOL. PER CENT	MCV	MCHC	NUMBER OF PATIENTS
		per cent	*grams*						
Males									
First	4.6	81.8	12.8	9.1	31.8	38.1	84.9	35.2	56
Second	4.2	74.4	11.6	9.0	26.2	35.0	75.7	34.0	34
Third	4.2	73.9	11.5	9.5	15.5	32.7	71.0	37.3	11
Females									
First	4.7	83.5	13.0	10.4	30.1	40.0	90.1	32.3	40
Second	4.0	74.3	11.6	9.7	39.2	33.4	82.8	33.9	23
Third	4.1	71.5	11.1	7.7	33.8	32.0	78.1	34.1	10

S.I. = sedimentation index. MCV = mean corpuscular volume. MCHC = mean corpuscular haemoglobin concentration.

seventh stage of operation is so long that the patient has had sufficient time for proper haematopoiesis.

In some cases a drop in the white blood cell count and in the sedimentation index of the red blood corpuscles occurs before the third stage of thoracoplasty. The sedimentation index (S.I.) during an operative course is usually an unreliable indicator of the effectiveness of thoracoplasty. Often it becomes more elevated because of the absorption of tissue products from the operative wound and from the immediate effects of collapse therapy upon tuberculous disease.

Table 2 further reveals that, even though the red cell count and size and the haemoglobin all decrease, still the amount of haemoglobin distributed through-

out the red cell mass (the MCHC) remains within or near the minimum of the range of normal. This should still be interpreted as actual anaemia. The mass of haemoglobin is now distributed to a reduced number of smaller sized (microcytic) red corpuscles.

TABLE 3

Haemogram showing the effects of thoracoplasty on a group of patients not treated by anti-anaemia measures

STAGE	RBC	Hgb		NUMBER OF PATIENTS
				Males
		per cent	*grams*	
First	4.9	82.6	12.9	9
Second	3.6	66.8	10.5	9
Third	3.9	70.0	10.9	2
				Females
First	4.1	76.0	11.9	15
Second	3.6	66.0	10.3	13
Third	3.8	62.1	9.7	5

TABLE 4

Haemogram showing the effects of thoracoplasty on a group of patients treated by anti-anaemia measures

STAGE	RBC	Hgb		NUMBER OF PATIENTS
				Males
		per cent	*grams*	
First	4.3	83.8	13.1	24
Second	3.9	79.9	12.5	24
Third	4.2	82.4	12.8	19
				Females
First	4.3	82.4	12.8	25
Second	3.9	78.1	12.2	25
Third	4.1	77.2	12.0	20

Microcytosis appears in both the untreated and the treated groups following each stage of thoracoplasty. The haematopoietic system lags primarily in haemoglobin production and secondarily in the size and number of the red corpuscles produced.

The treated patients fared better, when judged symptomatically and by laboratory studies (tables 3 and 4), than those who were not so treated by anti-anaemia measures.

TREATMENT

Earlier it was mentioned that, from the beginning of this study, the interns and the residents of the surgical services were not requested to search for or instructed to treat any of the anaemia associated with thoracoplasty patients. Such was the case from April, 1934 to June, 1939. During this period it was noted that more often than not the patient's anaemia attracted attention by clinical observation first and then would be confirmed by laboratory means. This observation occurred usually after the second or third stage. Then treatment was started. Usually heavy doses of either iron and ammonium citrate or Blaud's pills, a high caloric and a high vitamin diet were given. Sometimes a high caloric and a high vitamin diet were ordered at the time of admission to the surgical service.

In the period from June, 1939 through June, 1941 the anaemic patients on admission to a surgical service were treated more energetically. They were started on a high caloric, high protein and high vitamin diet. By the latter is meant: 3,000 calories daily, 100 to 125 g. of protein daily and liberal amounts of fresh vegetables and fresh fruit juices. Iron was given by mouth after meals three times daily (sodium ferric citrate grains 14; after June, 1939 it was ferrous sulphate grains 3, three times daily after meals). This was supplemented by the use of brewer's yeast tablets grains $7\frac{1}{2}$ three times daily after meals. Some patients received, at their own request, codliver oil and tomato juice three times daily.

Beginning in December, 1939 all thoracoplasty patients were placed on a routine for treatment and laboratory observation of the blood picture. They were given the diet mentioned above. Ferrous sulphate, grains 3, and brewer's yeast tablets grains $7\frac{1}{2}$, were given three times daily and at bed-time. These tablets were continued daily between stages of operation and for as long after the last stage as the blood picture indicated. All thoracoplasty patients had a red blood corpuscle and haemoglobin determination the day before and three days after each stage of operation. One month after the last stage, each patient had a red cell count and a haemoglobin estimation. If anaemia persisted, then treatment for this was continued. As soon as thoracoplasty was decided upon, each patient was started on a routine of diet, anti-anaemia treatment and close and frequent laboratory follow-up of the red cells and haemoglobin.

Since June, 1941 it has been found that larger doses of iron (ferrous sulphate, grains 6, three times daily and at bed-time) and brewer's yeast tablets' (grains 15, three times daily and at bed-time) give better results from every angle.

If all the anaemic and border-line patients were adequately and vigorously prepared two or three months in advance of their first stage of thoracoplasty, the results of anti-anaemia treatment would certainly be more encouraging. This should not be difficult since usually we know two or three months in advance the time of each patient's operation.

One should not be satisfied with the minimum of the normal range for the red blood corpuscles and haemoglobin. The goal should be the maximum of the normal range. In this way the number of anaemic or "border-line" patients who

approach their first stage of thoracoplasty will be much less. Their levels of red cells and haemoglobin will not be so easily or seriously lowered despite repeated operations. It is better to have the drop postoperatively in the range of normal for red cells and haemoglobin. Anti-anaemia therapy should be continued adequately and vigorously between each stage and frequently for two or three months after the last stage. The correction of anaemia is inexpensive and easy.

The necessity of routine blood transfusions postoperatively can be infrequent. An adequate anti-anaemia therapy course started well enough in advance of thoracoplasty and continued through and after the operative course will be sufficient preparation in the vast majority of cases.

DISCUSSION

The reasons for the development of the anaemia of thoracoplasty are interesting. The few sections of ribs removed at operations probably do not constitute a serious threat to haematopoiesis. The blood lost with each stage appears to explain most of the postoperative anaemia. Blood-loss replacement is said to be rapid. Nevertheless, in the two to three week interval between stages, red cell and haemoglobin values do not return completely to their preoperative levels.

In 8 patients red blood cell counts and haemoglobin determinations were done just prior to and within twenty-four hours of each stage. The greatest drop invariably occurred in the immediate postoperative period. This indicates haemorrhage as an important cause of postoperative anemia.

The effects of anaesthesia upon blood formation and destruction are noteworthy. Ether was rarely used during these operations. As for nitrous oxide, its effect upon haematopoiesis can be discounted.

The following quotations are pertinent. "Poggiolini (2) investigated the morphological changes of the blood, in ether and chloroform narcosis, in a series of experiments upon healthy rabbits. The changes of the blood constituents, noted after ether or chloroform narcosis, are independent of the duration of the narcosis, of the quantity of the narcotic, of the frequency of the narcosis, and of the time-interval between the individual narcoses. Deep narcosis, with ether or chloroform, induces leukocytosis, of variable duration and degree. The red blood corpuscles and the haemoglobin present rather variable changes, independent of each other, after the two narcoses. However, after chloroform narcosis there are regular destructive and retrogressive changes of the red blood corpuscle, which are absent after ether narcosis. Accordingly, inhaled chloroform appears to be more toxic, and of a more prolonged action, than ether, in the opinion of Poggiolini".

Then there is the factor of reduced food intake for two or three days postoperatively. This is repeated two or three or more times during a thoracoplasty course. Postoperative anorexia and vomiting add to the difficulties temporarily. A diminished nutritional reserve for haematopoiesis becomes inevitable.

Preoperative and postoperative dehydration and hydraemia probably do not

affect appreciably the number of circulating formed elements. With modern operative preparation to rely on, body fluids, blood sugar and sodium chloride are kept at normal levels.

In 1931 Aronson (3) reported on the specific cytotoxic action of tuberculin on tissue cultures. He studied explants of bone marrow of tuberculous and non-tuberculous guinea pigs, using varying strengths of tuberculin for different periods of time. His conclusions are: "Tuberculin from the human and from the bovine type of tubercle bacilli inhibits the growth of cells from explants of bone, spleen and testes of tuberculous guinea pigs and is toxic for these cells, but has no effect on explants of the same tissues from nontuberculous animals." This work has been confirmed by Rich and Lewis (4) and Moen and Swift (5).

This experimental evidence offers at least a partial explanation of the development of postoperative anaemia due to autotuberculinization. Tuttle (6) believed this phenomenon to be as frequent as 20 per cent postoperatively. However, it leaves the 80 per cent group in need of an explanation of their anaemia.

The effects upon the haematopoietic system of autotuberculinization following collapse therapy would be comparable to that resulting from any acute infection or intoxication. In a well fibrosed case of pulmonary tuberculosis it is probably not of any serious consequence.

Chronic infection does inhibit haematopoiesis. Its effects on blood formation are manifest before thoracoplasty is indicated. Such effects become more pronounced after stages of operation. Operative interference as a cause of more marked anaemia is distinct aetiologically from chronic infection alone.

In recapitulation, the factors enumerated above are accumulative in their effects on blood formation. A good number of tuberculous patients come to their first stage of thoracoplasty with some degree of hypochromic anaemia and microcytosis. They have been burdened by chronic infection for months or years. Their haematopoietic system has had to withstand the brunt of repeated inhibitive effects of intoxications. The added burden of operations is sufficient to increase the incidence of the anaemia associated with pulmonary tuberculosis. This incidence amounts to 85 per cent of all the operated patients, if we rightfully take into account the border-line cases as well.

Of the complications mentioned above, tuberculous empyema affected red blood corpuscle and haemoglobin levels most and the anaemia was most marked in this group. The other complications were treated, and intestinal tuberculosis particularly controlled well in advance of the first stage of thoracoplasty.

SUMMARY

Microcytic hypochromic anaemia was observed often before thoracoplasty in a group of 143 tuberculous patients. Its incidence increases rapidly with each stage of thoracoplasty. After a third stage, anaemia appears in as many as 85 per cent. The aetiology of this anaemia is discussed. The causes usually have the following order of appearance in the tuberculous patient who comes to thoracoplasty: chronic infection, complications of one kind or another, inade-

quate anti-anaemia control at all times and, most important, repeated operative blood losses and postoperative anorexia and emesis.

A detailed method of the control and correction of this anaemia is outlined.

The aim in the anti-anaemia treatment of the pre- and postoperative patients is to reach normal red cell count and haemoglobin values. The necessity for frequent blood transfusions postoperatively should become quite seldom.

SUMARIO

En un grupo de 143 tuberculosos se observó a menudo anemia hipocrómica microcitaria antes de la toracoplastia. Su frecuencia aumenta rápidamente con cada tiempo de la operación, y después del tercer período se presenta hasta en 85 por ciento. Discútese la etiología de esta anemia. En los tuberculosos que se presentan para toracoplastia las causas que suelen intervenir siguen el siguiente orden en su aparición: infección crónica; complicaciones de un género u otro; insuficientes medidas antianémicas en todas ocasiones; y, lo que es más importante, repetidas pérdidas sanguíneas, debidas a la operación, y anorexia y emesis postoperatoria.

Discútese con todo pormenor un método para cohibir y corregir esta anemia. El propósito en el tratamiento pre- y postoperatorio de la anemia consiste en alcanzar fórmulas normales de hematíes y hemoglobina, debiendo así hacerse rarísima la necesidad de utilizar postoperatoriamente frecuentes transfusiones sanguíneas.

The author is grateful to Drs. Sumner H. Remick, Harlan F. Newton, H. Stuart Willis, E. J. O'Brien, William M. Tuttle, Raphael Isaacs and Joseph Kasper and the members of the medical and surgical staff of the above mentioned institutions for their kindnesses and coöperation.

REFERENCES

(1) Braverman, Morris M.: The anaemia of pulmonary tuberculosis, Am. Rev. Tuberc., 1938, *38*, 466.

(2) Poggiolini: Le modificationi morphologiche del sangue nella narcosi eterea e nella cloronarcosi, Il Policlinico, 1911, Sez. Chir., 18, 3–5, quoted by Gwathmey, J. T.: Anesthesia, second revised edition, The Macmillan Co., 1924, p. 58.

(3) Aronson, J. D.: The specific cytotoxic action of tuberculin in tissue culture, J. Exper. Med., 1931, *54*, 387.

(4) Rich, A. R., and Lewis, M. R.: The nature of allergy in tuberculosis as revealed by tissue culture studies, Bull. Johns Hopkins Hosp., 1932, *50*, 115.

(5) Moen, J. K., and Swift, H. F.: Tissue culture studies on bacterial hypersensitivity, I. Tuberculin sensitive tissues, J. Exper. Med., 1936, *64*, 339.

(6) Tuttle, William, M.: Personal communication.

THE ELECTROCARDIOGRAM IN PULMONARY TUBERCULOSIS[1]

I. The Clinical Significance of Concordant Inverted Initial Ventricular Deflections in Patients with Chronic Pulmonary Tuberculosis

SIDNEY P. SCHWARTZ AND HENRIETTE MARCUS

The purpose of this study was to determine the clinical significance of the electrocardiograms obtained on patients with chronic pulmonary tuberculosis in whom the initial ventricular deflections in the standard leads were directed downwards. Attempts were made to correlate the clinical manifestations which these patients presented during their stay at our institution with roentgenograms, electrocardiograms and necropsy findings. Comparisons were made between the clinical course of the patients who showed this type of electrocardiographic pattern with patients who showed similar records but in the absence of pulmonary tuberculosis.

With the exception of some sporadic observations in which such records were noted in the course of an acute coronary artery occlusion (1, 2) or discussed as a possible unusual form of bundle branch block (3), the observations of Burstein and Ellenbogen (4) are the only ones in the literature where an attempt was made to correlate this type of electrocardiogram with some underlying pathological lesion of the heart. Unfortunately their studies lack the support of necropsy findings which are so essential for an understanding of these abnormal electrocardiograms if any value is to be found in their recognition during the course of a patient's illness.

They found 9 such records in a series of 15,000 electrocardiograms. Their first case may be discounted since the downwardly directed initial ventricular deflections were associated with complete auriculo-ventricular dissociation. In the presence of this type of heart block, it is well established that the fatigue of one bundle in the course of the idio-ventricular beating heart may cause the other bundle to assume the pace-maker of the heart and consequently yield a differently directed ventricular complex from moment to moment. Of the 8 remaining cases, 3 had recent coronary artery occlusions and in 3 others this was regarded as the most likely cause. Six of the 8 patients gave a history of bronchiectasis or some other chronic pulmonary disease. Four patients had pleural effusions at the time the records were obtained and in 2 patients pericardial effusion was suspected.

The transient nature of the downwardly directed deflections in 4 of their patients was attributed to the presence of either pleural or pericardial effusions, since with the absorption of the fluid from these spaces, there was a return to the normal type of electrocardiogram. Note should be made here of the unusually low voltage of some of their records which makes the recognition of the QRS complex in lead 1 very difficult.

[1] From the Cardiographic Laboratory and the Division of Pulmonary Diseases, Montefiore Hospital for Chronic Diseases, New York City.

They concluded that in their patients the alterations in the electrical contacts between the heart and the conductors about it seemed to have much to do with causing the downward direction of the ventricular deflections especially in those patients in whom the configuration became normal following the disappearance of the pleural or pericardial effusion. They felt, however, that the changes in the heart muscle proper interfering with the spread of impulses must have played a part in determining this pattern.

Very recently Katz (5) published 3 examples of this type of electrocardiogram which he thought were definitely abnormal but their significance was not clear to him. No mention is made by him of the type of patient in whom these records were obtained.

Our own files contain 7 electrocardiograms of concordant downwardly directed initial ventricular deflections in patients with pulmonary tuberculosis. There were 2 such records obtained on patients with congenital malformations of the heart and 5 were found in patients with infarction of the heart. One record was found in a patient with cylindrical bronchiectasis and long standing chronic bronchitis with asthma. Only 15 electrocardiograms with concordant downward directed initial ventricular deflections were found in a series of 24,200 records obtained at the Montefiore Hospital over a period of ten years, 362 of which were on patients with chronic pulmonary tuberculosis. The patients whose records were found to have been associated with pulmonary tuberculosis are described here in detail.

REPORT OF CASES

Case 1: H. S. (History No. 22626), a male, aged sixty-three years, was admitted to the Hospital on November 7, 1930 and died on August 27, 1933. His present illness dates back thirty-five years when he developed cough with expectoration. In June, 1930 he experienced a painful swelling of the scrotum which had to be incised. His sputum was found positive for tubercle bacilli in September, 1930.

Physical examination on admission to the Hospital revealed a poorly nourished old man who showed an emphysematous type of fibroid pthisis with a cavity in the right upper lobe. Diffuse bronchiectasis throughout both lower lobes was confirmed by roentgenograms. In February, 1932, the patient began to experience increasing dyspnoea and cyanosis. He complained of pain and tenderness in the mid-epigastric region with frequency in urination and nocturia. His heart was approximately normal in size, shape and position. The heart sounds were of good quality. There were no murmurs and no accentuation of the basal heart sounds. His blood pressure was 125/80. The edge of the liver was not palpable and there was no oedema of the lower extremities. An electrocardiogram obtained at this time revealed left axis deviation, a lowered voltage of the main ventricular deflections and a relatively slow ventricular rate in the presence of sinus rhythm (figure 1-A).

During the ensuing months, his cough became progressively worse, his dyspnoea and cyanosis increased, his liver became larger, oedema of the lower extremities appeared and there was now a uniform increase in the size of the heart as judged from comparative roentgenograms. The blood pressure remained the same. An electrocardiogram obtained on September 29, 1932 showed a concordant inverted type of initial ventricular deflection with no evidences of intraventricular conduction disturbance and a moder-

ately high voltage of the main ventricular deflections. In lead 3 there was one R-wave which was positive and very likely the result of a respiratory change. Particular note was made here of the lowered R–T segment with the negative T-wave in lead 3 (figure 1-B). Despite the use of dietary restrictions, mercurial diuretics and digitalis, this patient became progressively worse during the next year. There was a further increase in his cyanosis, dyspnoea and signs of congestive heart failure with a progressive enlargement of the heart as judged by comparison roentgenograms.

Repeated electrocardiograms revealed no other changes except that now, May 29, 1933, the previously downwardly directed initial ventricular deflections persisted in their pattern until the patient's death from cardiac failure in the course of his long standing pulmonary disease (figure 1-C).

Necropsy findings revealed the pericardial cavity to be normal. The pleural spaces were free from fluid. The heart was enlarged and weighed 450 g. The left ventricle measured 10 mm. in thickness and the right varied from 6 to 8 mm. The anterior surface of the heart was formed by the main portion of the right ventricle and the pulmonic

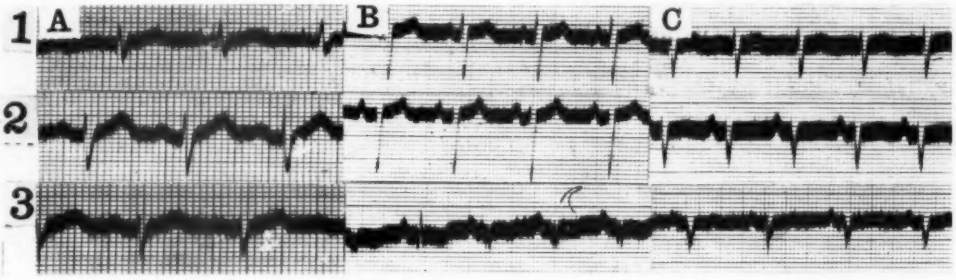


FIG. 1. Case 1. (A) Control record showing left axis deviation. (B) The main ventricular deflections are now downwardly directed. In lead 3, the S-T segment is below the iso-electric line, and the T-wave is negative. R_3 is frequently positive because of the influence of respiration. (C) Note the uniform lowering of the voltage of the QRS complexes as compared with B.

conus which was markedly dilated. The septum bulged to the left. The papillary muscles of the right ventricle were markedly hypertrophied and their trabeculae flattened. The coronary arteries were normal. The left lung revealed a large cavity with several caseous nodules averaging 2 cm. in diameters. There were numerable emphysematous blebs in the upper lobe while the rest of the lung was voluminous, firm and covered with fibrinous tags. The right lung also had numerous caseous nodules measuring 1 cm. in diameter and upper lobe bronchiectasis. There was chronic passive congestion of the lungs, liver, spleen and gastro-intestinal tract and a moderate nephrosclerotic picture of the arterial and arteriolar type in the kidneys.

Microscopic examination of the various portions of the heart showed the muscle cells of the left ventricle to be slightly enlarged. There was moderate subendocardial fibrosis with slight fatty infiltration of the coats of the vessels. The right ventricle showed a chronic inflammation of the epicardium with granulation tissue. There was an accumulation of oval shaped endothelial cells around one of the larger veins. The coronary arteries were soft and patent.

Comment: In a patient with an emphysematous type of chronic fibroid pthisis, there were progressive signs of congestive heart failure with an increase in the

size of the heart as judged from comparison roentgenograms. A control electrocardiogram obtained before the onset of failure revealed left axis deviation. With the first increase in the size of the heart and the appearance of congestive heart failure, the electrocardiogram changed to one in which the main ventricular deflections were downwardly directed and the S-T segment in lead 3 was lowered below the iso-electric line. A further progression in the signs of congestive heart failure and increase in the heart shadow coincided with a slight lowering of the voltage of the initial ventricular deflections but with a change to positive of the T-wave in lead 3. The pattern of downwardly directed ventricular deflections was *permanent* and the duration of the patient's life was one year after its appearance.

Case 2: E. B. (History No. 25213), a male, aged twenty-three years, first showed signs and symptoms of tuberculosis in 1929. On October 6, 1931 he had the last stage of a thoracoplasty which was preceded by repeated pneumothoraces on the left side. He entered Bedford Hills Sanatorium on May 16, 1932 where he showed a productive tuberculous lesion involving the entire left lung with cavitation in the infraclavicular region. He was transferred to the Montefiore Hospital on January 14, 1935 and died on June 8, 1935.

Physical examination on admission revealed him to be dyspnoeic. He showed a scoliosis with convexity to the left. The apical impulse of the heart was displaced towards the second intercostal space 5 cm. from the mid-clavicular line. It was diffuse and the heart sounds were of good quality. There were no murmurs. The blood pressure was 110/80. The right lung presented a nodular exudative dissemination throughout. The left lung was collapsed by an old thoracoplasty. The edge of the liver was not palpable and there was no oedema of the lower extremities. An electrocardiogram obtained on April 10, 1935 revealed right axis deviation with no evidence of any ventricular strain.

In the following month, the lung lesion progressed, the patient became more dyspnoeic and the cyanosis was more pronounced. He began to experience recurrent attacks of shortness of breath associated with heart rates averaging 156 beats per minute and profuse perspiration. These would last from fifteen minutes to an hour at a time. No other evidence of congestive heart failure was present. The liver edge was not palpable. An electrocardiogram obtained three days before his death reveals a concordant inverted form of QRS complex in all three leads.

At necropsy, 40 cc. of clear straw colored fluid was found in the pericardial sac. The lower portion of the left pleural cavity contained a few teaspoonfuls of pus but there was a larger thickened pleura over the left lung which was shrunken and contracted upwards. The heart weighed 260 g. The left ventricular wall was 12 mm. thick, the right ventricle measured only 3 mm. and was markedly dilated. It formed four-fifths of the anterior surface of the heart. There was slight hypertrophy of the pulmonary conus. The auricles were normal in size. The valves and endocardium were smooth. The right lung revealed discrete grayish nodules which appeared more confluent in the apical portion. The bronchi and bronchioles of both lungs were markedly dilated and their cavities were lined with smooth mucosa. The left lung had an ovoid cavity 4 inches long and 1 inch wide. The liver showed a central type of congestion with moderately severe clouding.

Microscopic examination of both ventricles revealed no evidence of hypertrophy of

the individual muscle fibres and sections of the coronary vessels showed no intimal changes.

Comment: In a patient who had a thoracoplasty performed for the collapse of a large cavity in the left upper lobe, the electrocardiogram on admission revealed right axis deviation. With progression of the tuberculous process, signs and symptoms suggestive of cardiac involvement appeared. Peculiar attacks consisting of recurrent seizures of dyspnoea, tachycardia and cyanosis occurred frequently, although evidence of congestive heart failure, such as an enlarged liver and oedema of the extremities, was absent. The electrocardiogram shortly before death revealed a concordant type of inverted QRS deflection.

Necropsy showed a dilatation of the right ventricle in the absence of hypertrophy of the chamber. The small amounts of free fluid in the pericardial and pleural sacs were negligible. The patient lived only three days after the appearance of this pattern of downwardly directed ventricular deflections.

Case 3: E. H. (History No. 25913), a female, aged forty-nine years, was admitted to the Hospital on July 18, 1935 and died on December 8, 1935. Her illness dates back to 1924 when she had to be tapped for pleurisy on four separate occasions. Six years ago she experienced her first haemoptysis. From then on she became progressively worse and complained of recurrent attacks of palpitation associated with shortness of breath.

Physical examination on admission revealed an emaciated, dyspnoeic and pale woman who showed extensive dissemination of small tubercles throughout all lobes with a cavity in the right upper lobe. Her heart was small and approximately normal in size, shape and position (figure 2). The heart sounds were of good quality. There were no murmurs. The blood pressure was 110/85. The liver and spleen were not palpable and there was no oedema of the lower extremities.

During her first month in the hospital her dyspnoea and cyanosis became progressively worse. She required the constant administration of oxygen for relief. However, her liver was not enlarged and she showed no oedema of the lower extremities or any other evidence of congestive heart failure except some distention of the neck veins. An electrocardiogram obtained at this time revealed a concordant inverted type of QRS complex in the three standard leads without changes in any of the RS-T segments (figure 2-A).

In the ensuing months the patient became more dyspnoeic and showed increasing cyanosis despite the constant use of oxygen. Repeated roentgenograms and fluoroscopic examinations of the chest showed no increase in the heart shadow or any enlargement of the individual cardiac chambers but there was a definite change in the electrocardiogram obtained on October 19, 1935 which persisted until the patient died in coma on December 8, 1935. This record showed, in addition to the downwardly directed ventricular deflections, an upward bowing of the S-T segment in lead 2 and a lowering of the S-T segment below the iso-electric line in lead 3 with inversion of the T-waves in both of these leads (figure 2-B).

Necropsy findings revealed the pleural and pericardial cavities to be free from fluid. The heart weighed 280 g. The left ventricle was 12 mm. thick and the right measured 3 mm. and was dilated. The papillary muscles and trabeculations of the right ventricle were large and prominent. The coronary arteries were thin walled. The lungs were equally large and showed considerable emphysema. Both presented innumerable pinhead sized nodules and the right upper lobe showed large caseous tubercles with an irregu-

lar thick-walled cavity. A good deal of the lung was atelectatic and emphysematous and microscopical examination showed caseous bronchitis throughout. The liver and spleen showed signs of chronic passive congestion, although the organs themselves were not enlarged. Microscopical examination of the heart muscle fibres did not reveal any hypertrophy.

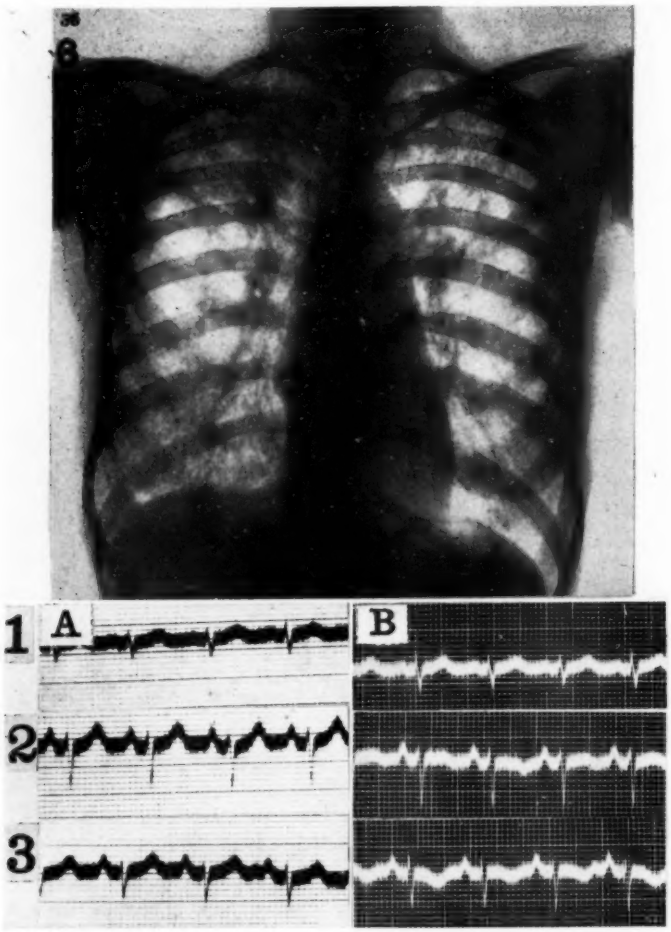


FIG. 2. Case 3. (A) On admission the electrocardiograms revealed downwardly directed ventricular deflections. (B) Note the lowering of S-T segments and negativity of the T-waves in leads 2 and 3 as an index of further strain upon the right ventricle.

Comment: In a patient with dyspnoea and cyanosis as the most pressing symptom, and electrocardiogram on admission revealed a concordant inverted type of QRS deflection. A further increase in her symptoms resulting from dissemination of the tuberculous process yielded changes in the S-T segments of leads 2 and 3 but the downwardly directed deflections remained the same. At necropsy the right ventricle was dilated but not hypertrophied and there were no abnormal microscopical changes in the heart muscle proper.

Case 4: B. K. (History No. 27188), a male, aged fifty-eight years, was admitted to the Hospital on October 3, 1936 and died on October 12, 1936. He was ill for the first time eight years ago. During the past year he became progressively short of breath and orthopnoeic. In July, 1936, both feet were swollen but this subsided after a few weeks of red-rest. Six weeks ago he had a severe attack of dyspnoea, associated with intense cyanosis but he improved sufficiently to go home and rest until his admission here.

Physical examination showed him to be afebrile but very dyspnoeic. The superficial veins of the neck were dilated. The right chest was larger than the left. The left border of the heart was displaced 2 cm. to the left of the mid-clavicular line. The heart sounds were of good quality but there were no murmurs. The blood pressure was 80/50. The liver edge was barely palpable. Roentgenograms of the chest revealed both upper lobes to be honey-combed with innumerable cavities many of which were bronchiectatic. There was also an extensive consolidation of the left lower lobe. It was impossible to delineate the outline of the heart which was distorted by adhesions to the surrounding tissues.

A single electrocardiogram taken on admission revealed a concordant inverted type of QRS complex with large P waves in leads 2 and 3. The voltage of the main ventricular deflections was low. In lead 4 there was a diminished R-wave with elevation of the S-T segment above the iso-electric line and a positive T-wave.

At necropsy no free fluid was found in either the pleural or pericardial cavities. The pleura was markedly thickened and fibrotic. The left lung was reduced to one-half the size of the right lung. It showed saccular dilatation of the large bronchi with almost complete disappearance of parenchyma. The heart weighed 400 g. The left ventricular wall was 15 mm. thick and the right was 10 mm. The right side of the heart was unusually prominent and firm. The right auricle was dilated. The thickness of the right ventricular wall together with its trabeculae and papillary muscles was markedly increased. The outflow tract of the right ventricle was particularly dilated. The coronary vessels were smooth and thin. The liver and spleen showed marked passive congestion, although these organs were comparatively small. Microscopical examination of the heart revealed hypertrophy of the individual fibres of the right ventricle but nothing else of significance.

Comment: In a cyanotic and dyspnoeic patient without clinical evidences of congestive heart failure, the electrocardiograms revealed a concordant inverted type of initial ventricular deflection with elevation of the S-T segment in lead 4. In the absence of pleural and pericardial fluid the right heart was found enlarged and the right ventricle markedly hypertrophied.

Case 5: M. Z. (History No. 21298), a female, aged forty-nine years, was transferred from Bedford Hills Sanatorium to the Montefiore Hospital on May 22, 1933 and died on November 4, 1933. She was known to have tuberculosis since 1915.

Her chief complaint was palpitations of the heart, although her blood pressure was only 116/94 and roentgen examination of the chest revealed the heart to be approximately normal in size, shape and position but slightly drawn to the right by mediastinal adhesions. Because of her progressive dyspnoea and orthopnoea, wheezing respirations and cyanosis, an electrocardiogram was taken on May 8, 1933 and this showed merely left axis deviation. In the next few weeks she became progressively worse. She developed marked dyspnoea at the least exertion but there was no distention of the neck veins. Indeed most of her symptoms and signs were attributed to a progression of her tuberculosis

even though orthopnoea became alarming. A comparison electrocardiogram obtained on June 24, 1933 showed a concordant type of inverted QRS deflection in all 3 leads. Three days later she developed marked cardiac enlargement as visualized in the roentgenograms with distention of the neck veins, increasing ascites and anasarca. The liver edge descended to the umbilicus in less than one day.

She became more comfortable following the use of diuretics until she developed a thrombosis of the left subclavian vein on August 21, 1933. This extended into the left axillary vein and she died in a severely dyspnoeic state on November 4, 1933.

At necropsy her heart was found to weigh 300 g. The left ventricle was 10 mm. thick whereas the right measured 6 mm. and formed the anterior aspect of the heart. It was both hypertrophied and dilated and its papillary muscles were large and flattened. The right auricle was likewise dilated and its wall was thickened. There was no free fluid in the pleural or pericardial sacs but there was slight ascites. The lungs were voluminous and there were adhesions between the left lung and its pleural covering and the entire left upper lobe consisted of bronchiectatic cavities. The right pleura was thickened and many of the small arteries of the right lung were thrombosed. There were innumerable small bronchiectatic cavities with large emphysematous blebs in the upper lobe of the right lung. The liver revealed a perihepatitis with marked passive congestion. Microscopical examination of the heart revealed only hypertrophy of the muscle fibres of the right ventricle.

Comment: A woman with far advanced pulmonary tuberculosis, who showed on admission to the hospital an electrocardiogram with left axis deviation, developed a concordant type of inverted initial ventricular deflection simultaneously with an increase in the size of the heart as judged from comparison roentgenograms. This pattern persisted without any changes in the RS-T segments or T-waves for 6 months after its appearance when the patient died in severe congestive heart failure. At necropsy there was both hypertrophy and dilatation of the right ventricle.

Case 6: J. N. (History No. 26658R), a male, aged thirty-seven years, was transferred to the Montefiore Hospital from its Sanatorium on May 7, 1934 and several times during the ensuing years he came back and forth to the Hospital until his final admission in 1941 when he died in October of that year.

In 1935, he required a right pneumothorax. In March, 1936 he experienced a spontaneous rupture of the left lung after an attempt was made to introduce air in the left pleural cavity. Because of ineffectiveness, bilateral pneumothorax was discontinued in June, 1936. In February, 1938 he began to show increasing dyspnoea and from then on he was semi-ambulatory and had to remain in bed a good deal of the time. During his last year of illness he was extremely dyspnoeic and cyanotic. He had marked clubbing of the fingers. His chest was emphysematous. The apical impulse of his heart was in the fifth intercostal space in the mid-clavicular line. The heart sounds were of good quality. There were no murmurs audible. The blood pressure was 100/80. Serial roentgenograms of his chest revealed far advanced bilateral fibrocaseous disease with cavitation and marked emphysema. In the last few months of his life he developed a fluid level in one of his cavities.

He was now dyspnoeic out of all proportions to his physical signs. At times he had recurrent episodes of irregular breathing and frequently he experienced seizures of rapid breathing lasting from fifteen to thirty minutes at a time. His liver was not enlarged

and he showed no oedema of the lower extremities. Several electrocardiograms obtained on him revealed a concordant inverted type of initial ventricular deflection in all leads. The P-waves in leads 2 and 3 were very large (figure 3). The QRS complex in lead 4 was of the V-shape and R was totally absent. The S-T segment was abnormally elevated above the iso-electric line and the T-wave was negative. He died within six months after the appearance of this type of record.

Necropsy revealed chronic bilateral fibrocaseous pulmonary tuberculosis with cavitation. There was no free fluid in either the pericardial or pleural spaces. The pleura on both sides was obliterated by thick and firm adhesions and there was a slight fibrinous exudate over the auricles. The heart weighed 350 g. The pericardium was adherent over the left ventricle. The right ventricle was enormously enlarged and formed the anterior surface of the heart. It was 5.5 mm. thick while the left ventricle was 15 mm.

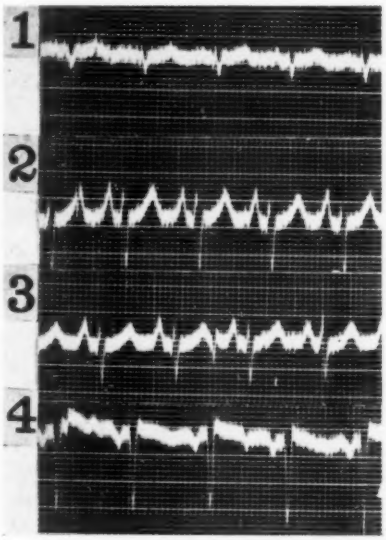


FIG. 3. Case 6. A record showing downwardly directed QRS complexes, large P-waves in leads 2 and 3 and the abnormal elevation with the downward sloping of the R-T segment in lead 4 indicating additional strain upon the right ventricle.

There was moderate dilatation of the pulmonic conus. The papillary muscles and trabeculae of the right ventricle were hypertrophied. The right auricle and its appendage were both dilated and hypertrophied. The tricuspid valve was displaced upwards and inwards by the hypertrophied tissue of the right ventricle, while the entire septum was distorted to the left as a result of this enlarged chamber. Microscopical examination of the heart muscle showed hypertrophy of the fibres of the right ventricle only.

Comment: In a patient with long standing chronic fibroid tuberculosis but without evidences of congestive heart failure and with a heart that appeared approximately normal in size, shape and position in the roentgenograms up to the last week of his life, repeated electrocardiograms revealed a concordant inverted type of initial ventricular deflection with large P-waves in leads 2 and 3 and abnormal S-T changes in lead 4. Necropsy revealed a markedly hypertrophied

and dilated right ventricle with dilatation of the right auricle in the absence of any free fluid in either the pericardial or pleural spaces.

Case 7: B. B. (History No. 32951), a male, aged forty-eight years, was admitted to the Montefiore Hospital on March 20, 1940 and discharged on March 8, 1941. He first became ill in 1927 with cough and sputum which was positive for tubercle bacilli. After a rest of three months, he returned to work and was well until 1930 when he suffered a remission of his symptoms. Since then he has been a semi-invalid.

Physical examination revealed a thin, chronically ill, pale man who was slightly dyspnoeic. His chest was emphysematous and roentgenograms revealed a very extensive fibrocaseous tuberculosis of both lungs with a greater extension on the right side. During his stay at the Hospital, he was ambulatory but his dyspnoea and cyanosis increased.

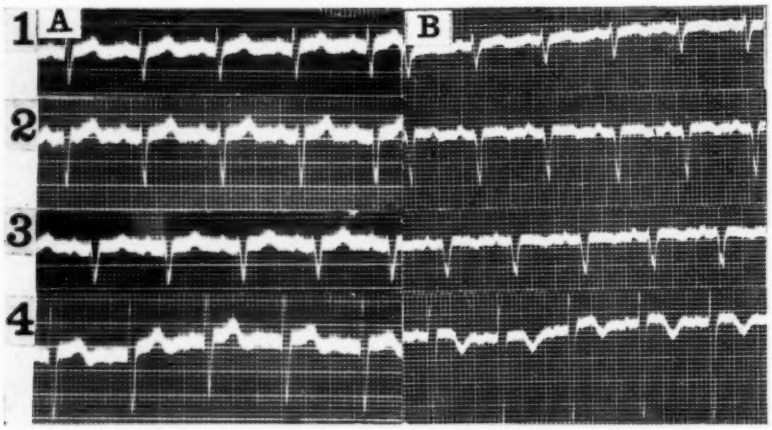


FIG. 4. Case 7. (A) The electrocardiogram on admission revealed the main ventricular deflections in all 4 leads to be downwardly directed. The T-waves were all positive. (B) Note the changes in T-wave negativity in leads 2, 3 and 4 indicating additional strain upon the right ventricle.

An electrocardiogram obtained on October 28, 1940 revealed a concordant inverted type of QRS complex with a positive T-wave in lead 4 (figure 4-A). In the succeeding months repeated records were obtained on him because of his increasing dyspnoea in the absence of other signs of congestive heart failure. The apical impulse of the heart was in the fifth intercostal space in the mid-clavicular line. The heart sounds were of good quality. There were no murmurs. The blood pressure was 118/80. The liver and spleen were not palpable. There was no oedema of the lower extremities. A comparison electrocardiogram obtained on January 22, 1941, at a time when he was intensely cyanotic and disoriented, revealed a change in the T-waves in leads, 2, 3 and 4 which were now inverted (figure 4-B). Although roentgenograms obtained at the same time showed no changes in the size of the heart, he became emotionally unstable and had to be transferred to a psychiatric institute.

Comment: In a patient with chronic pulmonary tuberculosis and with intense cyanosis and dyspnoea, progressive increase in these signs was associated with changes in the T-waves of an already concordant type of initial ventricular

deflection. Although necropsy was not available it is very likely that, as in the other cases, the electrocardiograms were the result of disturbances in the dynamics of the right ventricle.

DISCUSSION

These observations reveal that, in the course of chronic pulmonary tuberculosis, a small group of patients may develop a permanently established electrocardiogram with a concordant inverted type of initial ventricular deflection in the standard leads. In only 2 of the 7 patients studied was the appearance of this type of record associated with recognizable enlargement of the heart and frank signs of congestive heart failure. The clinical picture of the other 5 patients was predominantly one of a severe type of respiratory distress accompanied by intense cyanosis. In some of these patients there were recurrent attacks of shortness of breath lasting from fifteen to thirty minutes, with respirations averaging at times 40 per minute and with heart rates as rapid as 150 per minute. The symptoms resulting from diminished aeration in the course of pulmonary tuberculosis may be so similar to those resulting from circulatory failure secondary to the lung lesion, that it is extremely difficult at times to recognize which factor is responsible for the respiratory manifestations. Yet despite the paucity of signs of congestive heart failure in each instance exhibiting this electrocardiographic pattern during life, necropsy findings revealed some change in the size of the right ventricle either in the form of hypertrophy or dilatation. Frequently there was also enlargement of the right auricle.

It is therefore of more than academic interest to speculate on the factors responsible for the development of such electrocardiograms in patients with chronic pulmonary tuberculosis. In each one of our patients the pulmonary disease had been present for some time prior to the appearance of the downwardly directed deflections. The type of disease present and its duration apparently bear no relationship to the development of this pattern. Most students of this subject are agreed that signs of heart failure appear in the course of pulmonary tuberculosis when the amount of the parenchyma destroyed has reached a certain percentage of the total tissue (6). It is then that the increased pulmonary pressure yields changes in the cardiac chambers that may result in signs and symptoms of heart failure. The time factor in the development of signs of heart failure is unpredictable, since tuberculosis is a destructive disease that may run parallel with healing in the majority of instances.

There is very likely however some relationship between the type of disease in the lungs and the appearance of a lowered voltage of the main ventricular deflections even when they are already downwardly directed (see figure 1). In this respect only may it be said that the lung disease influences the conduction from the heart to the periphery directly. Obviously since none of our patients revealed fluid in either the pleural or pericardial spaces, this special factor may also be discounted as responsible for the downwardly directed initial ventricular deflections.

It would appear that a common factor present in all of our cases that may be

linked with the development of this electrocardiographic pattern would be *some increase in the size of the right ventricle, either hypertrophy or enlargement as a result of a dilatation of that chamber.* In this respect it is essential to appreciate that not all hearts of patients with chronic pulmonary tuberculosis need be hypertrophied before dilatation may take place. It is conceivable that transient changes in the size of the right ventricle may appear in the course of tuberculosis of the lungs as the pulmonary blood pressure rises with sufficient destruction of lung tissue. At times this process may be so rapid that the right ventricle has no time to hypertrophy. In other more chronic cases the actual hypertrophy may be almost as great as the thickness of the left ventricle. That hypertrophy may be present without dilatation as a result of an increase in the pulmonary pressure, as has been noted experimentally (7) and that signs of heart failure may be represented clinically in the form of dyspnoea alone is also a possibility. Yet in the present state of our knowledge of the failing heart in the tuberculous it must be admitted that there is no known method of recognizing sole hypertrophy of the right ventricle in the absence of dilatation. For this reason the recognition that this electrocardiographic pattern of downwardly directed initial ventricular deflections may be associated with such changes in the right ventricle becomes doubly important. It may be the only clue that the right ventricle is already implicated. Since this pattern has been found to persist and be irreversible and life is relatively shortened after its appearance, it may be a useful guide in the patient's prognosis.

Confirmation that hypertrophy alone without dilatation of the right ventricle may yield this pattern is gained from necropsy findings in patients with other conditions causing pulmonary hypertension who have died without evidences of congestive heart failure.

In one patient with congenital malformation of the heart and a pulmonic stenosis, the persistent presence of this pattern was found to have been associated with a very marked hypertrophy of the right ventricle but without any dilatation of that chamber, since repeated roentgenograms of the chest over a period of two years revealed no other change in the contour of the heart after the appearance of the downwardly directed deflections. This patient's only symptoms until death were extreme cyanosis and recurrent attacks of breathlessness at the least exertion. At necropsy there was no evidence of congestive heart failure in the systemic organs, death having occurred as a result of an intercurrent infection. Similarly another young female, aged twenty-eight years, with an Eisenmenger's syndrome and intense cyanosis experienced such breathlessness that she was confined to bed throughout her entire stay in the hospital for a period of three years after the appearance of the concordant inverted initial ventricular deflections. Her liver was never enlarged and she never showed any oedema of her lower extremities. At necropsy there was marked concentric hypertrophy of the right ventricle without any dilatation. In a third patient with bronchial asthma and cylindrical bronchiectasis of many years' duration the downwardly directed initial ventricular deflections persisted in the presence of a heart that appeared in the roentgenogram and on fluoroscopic examination

to be approximately normal in size, shape and position. This patient died from a superimposed infection of the lung. At necropsy the right ventricle was 8 mm. thick and the left ventricle measured only 10 mm. Congestion of the liver was not present.

Yet it must be noted from these observations that this pattern may be likewise present with a very small heart and a small right ventricle but one which dilated very rapidly as the pulmonary pressure is suddenly increased in the course of rapid destruction of the lung tissue. In such cases (cases 3, 6 and 7) additional electrocardiographic evidences of acute dilatation of the right chambers of the heart may be gained from the large P-waves in leads 2 and 3 that are an index of right auricular dilatation; from the significant changes in the RS-T segments present in leads 2 and 3 or in lead 3 alone and frequently from the changes which we are beginning to appreciate now as indices of right ventricular enlargement and strain in leads 4. These latter phenomenon have been amply confirmed by us in other patients with the failing heart in the course of tuberculosis (8).

If these observations prove to be correct then the downwardly directed type of main ventricular deflections may be said to be a stage of far advanced right ventricular strain in which either dilatation or hypertrophy of the right ventricle have so rotated the heart around its longitudinal axis that the pattern appears in the form described. Since abnormal deviations of this type fail to conform to Einthoven's triangle, it would be best to avoid further discussions for the theoretical reasons that cause these changes in the third lead in which the main ventricular deflection is invariably directed downward instead of upward as in the common type of right ventricular preponderance. There remains the problem of reconciling this type of electrocardiogram with the downwardly directed initial ventricular deflections that are encountered in the course of an acute or chronic infarction of the heart. It has already been stated that, in the presence of complete auriculo-ventricular dissociation, shifting of the ventricular complexes from right to left and vice versa may appear as a result of fatigue of one bundle so that the other assumes the pace-maker of the heart. In acute coronary artery occlusion with infarction and involvement of the bundle branches a similar phenomenon may take place in a transient form. This may explain such transient changes which have been wrongly attributed to the absorption of fluid from the pleural or pericardial sac (4) and clearly depend upon the state of circulation to the bundles of the heart. With improvement, these atypical bundle-branch pictures with their intraventricular conduction disturbances disappear. The more permanent patterns of downwardly directed deflections in the course of infarction of the heart are very likely the result of changes in the spread of impulses over abnormal pathways following either ischaemia or established circulatory disturbances to the conducting tissues. In each of the 5 instances that we have encountered in our own files the downwardly directed initial ventricular deflections following infarction of the heart have always presented a large or prominent Q-wave in lead 1 so that this distinguishing characteristic feature should easily differentiate those records that are not due to occlusion of a coronary artery with infarction provided the voltage is sufficiently

high to enable recognition of the Q wave. Most of Burstein and Ellenbogen's records show a prominent Q-wave in lead 1.

SUMMARY AND CONCLUSIONS

1. A study was made of the clinical significance of electrocardiograms showing a concordant type of inverted initial ventricular deflections in the standard leads in 7 patients with chronic pulmonary tuberculosis.

2. In 2 patients, the appearance of this pattern was associated with signs of congestive heart failure and recognizable enlargement of the heart as judged from comparison roentgenograms and fluoroscopic examination. In 5 patients the appearance of this pattern was found to be associated with symptoms of severe dyspnoea and cyanosis but with a relatively small heart in the roentgenograms.

3. In 3 patients, in addition to the downwardly directed QRS complexes there was enlargement of the P-waves in leads 2 and 3 and abnormal variation in the RS-T segment in leads 2, 3 and 4.

4. In 6 of the patients who came to necropsy this electrocardiographic pattern was found to be associated with either hypertrophy alone, hypertrophy and dilatation, or dilatation without hypertrophy of the right ventricle and occasionally the right auricle.

5. These correlated observations suggest that in patients with chronic pulmonary tuberculosis the appearance of downwardly directed deflections of the QRS complex are an index of changes in the muscle mass or the size of the right ventricle causing a rotation of the heart around its longitudinal axis.

6. Since respiratory distress and increasing cyanosis in patients with chronic pulmonary tuberculosis may be due either to the progression of the pulmonary lesion or to right heart failure in the absence of signs of congestion, this electrocardiographic pattern may be the only clue that the symptoms are the result of cardiac embarrassment.

7. This pattern being persistent and irreversible, its presence is of ominous prognostic significance. None of the patients with chronic pulmonary tuberculosis who showed it lived longer than one year.

SUMARIO Y CONCLUSIONES

1. Este estudio en siete enfermos de tuberculosis pulmonar crónica, versa sobre el significado clínico de los electrocardiogramas que revelan un tipo concordante de desviaciones ventriculares iniciales invertidas en las derivaciones clásicas.

2. En dos enfermos la aparición de este tipo se asoció a signos de insuficiencia cardíaca congestiva e hipertrofia reconocible del corazón, juzgados por roentgenogramas y exámenes fluoroscópicos comparados. En 5 la aparición de este tipo estaba asociada con síntomas de disnea y cianosis intensa, pero con un corazón relativamente pequeño, según el roentgenograma.

3. En 3 enfermos, además de los complejos QRS descendentes, había ensanche de las ondas P en las derivaciones 2 y 3, y variación anormal del segmento RS-T en las derivaciones 2, 3 y 4.

4. En 6 de los enfermos en que se realizó la autopsia, este tipo electrocardiográfico estaba asociado bien con hipertrofia sola, hipertrofia y dilatación, o dilatación sin hipertrofia del ventrículo derecho, y a veces de la aurícula derecha.

5. Estas observaciones correlacionadas indican que en los casos de tuberculosis pulmonar crónica la aparición de desviaciones descendentes del complejo QRS indica alteraciones de la masa muscular o del tamaño del ventrículo derecho, que hacen rotar el corazón alrededor de su eje longitudinal.

6. Dado que el malestar respiratorio y la cianosis creciente en los enfermos de tuberculosis pulmonar crónica pueden deberse bien a avance de la lesión pulmonar o a insuficiencia del corazón derecho, de no haber signos de congestión este tipo electrocardiográfico tal vez sea el único indicio de que los síntomas son efecto de la insuficiencia cardíaca.

7. Siendo este tipo persistente e irreversible, su presencia posee significado pronóstico de lo más grave, y ninguno de los enfermos de tuberculosis pulmonar crónica que lo reveló vivió más de un año.

REFERENCES

(1) Willius, F. A.: Clinical Electrocardiography, W. B. Saunders and Co., Philadelphia, 1929, pp. 193–197.

(2) Bainton, J., and Burstein, J.: Illustrative Electrocardiography, D. Appleton Century Co., New York, 1935, pp. 228–229.

(3) Wilson, F. N., Johnston, F. D., and Barker, P. S.: Electrocardiograms of an unusual type in right bundle branch block, Am. Heart J., 1934, *8*, 472.

(4) Burstein, J., and Ellenbogen, L.: Electrocardiograms in which the main ventricular deflections are directed downward in the standard leads, Ibid., 1938, *16*, 165.

(5) Katz, L. N.: Electrocardiography, Lea and Febiger, Philadelphia, 1941, p. 126.

(6) Griggs, D. E., Coggin, C. B., and Evans, N.: Right ventricular hypertrophy and congestive failure in chronic pulmonary disease, Am. Heart J., 1939, *17*, 681.

(7) Holman, E.: Hemicardiac hypertrophy due to increased peripheral resistance, J. Thoracic Surg., 1939–40, *9*, 263.

(8) Schwartz, S. P., and Marcus, H.: The electrocardiogram in chronic pulmonary tuberculosis, (III) The electrocardiogram in the failing heart of the tubercular, (to be published).

MANAGEMENT OF THE MINIMAL TUBERCULOUS LESION[1,2]

ALFRED L. KRUGER, BENJAMIN P. POTTER AND ABRAHAM E. JAFFIN

The literature abounds with advocates of the bed-rest regime for minimal lesions; all agree as to the importance of collapse measures in progressive and in the more advanced lesions (Kendall and Ross (1), Hegner (2), Brauer (3), Craig (4), Ringer (5), Potter (6), Hayes (7), Amberson (8), Baum (9), Webb (10), Gross and English (11)). Myers (12) emphasizes the importance of pneumothorax in progressive minimal lesions. On the other hand, there are those who subscribe to the immediate induction of collapse as soon as the diagnosis is made (O'Brien (13, 14) and Turner and Collins (15)). The latter school reasons that by so doing the lesion is brought under control much more quickly, thus eliminating all chance for dissemination to other parts of the lung fields and, in addition, increasing the chance of obtaining a free pleural space. Because of this controversy, we have analyzed all cases seen in the Hudson County Tuberculosis Hospital and Clinics between the years 1930 and 1939, inclusive. For this report, however, we have reviewed the X-ray films and records of those that have been persistently followed up to the time of the completion of the study.

In dividing the cases into hospital and clinic groups, we do not wish to create the impression that, at the beginning of this period of study, any attempt was made to select cases for either group. Rather, either because of lack of beds or because of failure of certain patients to heed the advice of the clinic physicians to enter the hospital, some were followed in the clinic, and so the two groups naturally evolved and offered a comparative study.

HOSPITAL CASES

There was a total of 87 cases, 58 of which we have classified as exudative and 29 as productive. By exudative, we mean that type of infiltrate that on X-ray films shows a flocculent or soft appearance with irregular margins and which on serial films shows a definite tendency to change. On the other hand, the productive infiltrate presents a firm, well delineated margin with a nodular or string-like appearance and which on serial X-ray films is of a stationary character. As might well be expected, because of the case-finding surveys conducted in Hudson County during the past three years, the majority of the minimal lesions are to be found in the latter three-year period of this study. We find, therefore, the follow-up period for the hospital cases was 3.5 years (3.4 years for the exudative lesions and 3.6 years for the productive ones). However, a few cases were followed as long as eleven years with a minimum observation period of one and one-half years.

As regards race, only 2 of the 87 cases were black. There were 57 females and

[1] From the Hudson County Tuberculosis Hospital, Dr. B. S. Pollak, Medical Director, Jersey City, New Jersey.

[2] Read before the Eastern Section, American Trudeau Society, in Jersey City, October 31, 1941.

30 males. Approximately 50 per cent of the entire group gave a positive family history for tuberculosis. As to the location of the lesion, 49 were on the right side, 36 on the left and 2 were bilateral.

CLINIC CASES

In this group, there was a total of 98 cases, 52 having an exudative and 46 a productive infiltrate. The new Hudson County Tuberculosis Hospital with its increased capacity was not opened until 1938, and so in the earlier years most of the minimal cases were not admitted to the hospital (due to the lack of beds) but were followed in the clinic with advice to rest in bed at home. Hence, the somewhat longer follow-up period in this group; 4.7 years for the exudative and 3.2 years for the productive lesions with an average of 3.9 years.

The nature of this group paralleled that of the hospital as to race (all white except for 3 black), sex (59 females as against 39 males), incidence of positive family history (46 per cent), and distribution of lesions (right lung 53, left lung 34, bilateral 11).

TABLE 1

Distribution of cases according to age-groups

AGE-GROUP	EXUDATIVE		PRODUCTIVE	
	Hospital	Clinic	Hospital	Clinic
years				
5–14	7	6	0	2
15–24	34	28	13	8
25–34	15	12	6	12
35–44	2	6	6	12
45–54	0	0	3	7
55–64	0	0	1	5

An analysis of the age-groups of both hospital and clinic patients (table 1) reveals that 78 per cent of the exudative lesion cases are to be found between the ages of ten and twenty-nine years. No case was found beyond the forty to forty-four year age-group. On the other hand, the productive lesion cases showed a fairly equal distribution throughout all age-groups.

Symptoms were noted in 48 of the 87 hospital cases and in 49 of the 98 clinic cases. The symptoms which were presented, in the order of their frequency, were productive cough, dry cough, chest pain, fatigue, weight loss and haemoptysis. Interestingly enough, only 2 patients in the entire group gave a history of weight loss and 2 others gave a history of bloody expectoration.

To present figures as to the incidence of positive sputum would be misleading, since in many instances in the early years of our study the sputum was not examined because of the absence of expectoration and in many others wholly inadequate quantitative and qualitative examinations were made of the available secretions. Prior to 1937 only an occasional patient had gastric lavage studies; and ever since then the search for tubercle bacilli in such specimens has been

reserved for the period prior to discharge when the original infiltrate had partly resorbed leaving a residual firm lesion not likely to yield organisms. This is similarly true of those cases in which a fair number of sputa was examined. From a public health point of view we consider adequate studies as judged by present standards essential prior to discharge whereas similar studies on admission seem to us to be, with very few exceptions in which a tuberculous aetiology of the lesion is doubted, of academic or confirmatory interest because the diagnosis is practically always obvious from clinical and roentgen examination of the patient. At the same time we wish to stress the fact that a more recent analysis made by us of the frequency of bacillary sputum in noncavernous tuberculosis, even after adequate search, fails to confirm the high incidence of positive results reported by some observers.

An analysis of the duration of hospital residence in relation to the type of lesion revealed that in the exudative group the time interval varied from one month (release) to eighteen months, the average being about eight months; the productive disease group ranged from one month (release) to nine months with an average of about four months. It has been our policy to hospitalize the latter group for at least three months. The reason for such a short period of hospitalization was that in practically all instances on initial examination the lesion was apparently controlled and this was subsequently confirmed during the hospital residence.

ANALYSIS OF RESULTS

A. Hospital Cases

1. Exudative lesion—58 cases
   a. Number treated effective by bed-rest—45 cases (78 per cent)
   b. Number progressed—13 cases (22 per cent)

Six showed progression of their lesion while in the hospital.

One showed no change but presented a positive gastric lavage on two occasions.

Six progressed twelve to thirty months after discharge. Three of these were in the hospital less than six months, one signed a release after four months, another refused to return to the clinic after discharge until thirty months later when she was admitted to another hospital and one, although he was treated for one year, had recurrence of the disease two years after discharge from the sanatorium.

Twelve of the 13 patients were readmitted to the hospital. Pneumothorax was induced in 11 in whom an effective collapse was obtained. The twelfth refused pneumothorax and so was placed on bed-rest with resolution of the infiltrate (no cavity was ever demonstrated) and she has since been followed in the clinic for four years with no change in the pulmonary lesion.

2. Productive lesion—29 cases
   a. Number treated effectively by bed-rest—28 cases (96 per cent)
   b. Number progressed—1 case (4 per cent)

This case had been in the hospital for four months with a stationary lesion. Because of the presence of a toxic goitre, a subtotal thyroidectomy was done. One month later a tiny cavity developed within the area of infiltrate and a positive sputum was obtained. Effective closure was obtained by phrenicectomy (no free pleural space on pneumothorax attempt).

Total cases treated effectively by bed-rest—73 or (84 per cent)
Total cases which showed progression—14 or (16 per cent)

B. Clinic Cases
   1. Exudative lesion—52 cases
      a. Number effectively treated by bed-rest—30 cases (58 per cent)
      b. Number progressed—22 cases (42 per cent)

Ten were seen once (at the time of the original diagnosis) and failed to return to the clinic until one to five years later at which time extension of the lesion was noted.
Twelve were followed in the clinic and showed progression of the lesion from one month to three years after the original diagnosis.
The present status of these patients is shown below:
Ten are receiving pneumothorax (8 unilateral and 2 bilateral), the collapse is effective in all and only one remains hospitalized.
In 5 the disease progressed to the moderately advanced stage and then became quiescent. All of these are well and working.
Four have open cavities.
The remaining 3 are dead.

   2. Productive lesions—46 cases
      a. Number effectively treated by bed-rest—46 cases (100 per cent)

Total cases treated effectively by bed-rest—76 or (77 per cent)
Total cases which showed progression—23 or (23 per cent)

DISCUSSION

We are in total agreement with the advocates of early collapse therapy in dealing with advanced tuberculosis. In the minimal stage of the disease, however, and as an initial procedure, we strongly indorse what Minor (16) said at the annual meeting of the American College of Physicians in March, 1928, in reviewing the evolution of the various therapeutic procedures in pulmonary tuberculosis:

"Of all the elements in the treatment of tuberculosis, there is one which must always take the first place whatever other methods are used in connection with it. I refer, of course, to the hygienic and dietetic treatment; and out of this method, so clearly laid down by its founders, and latterly so carefully studied in our sanatoria, there has slowly evolved the central idea of rest as the most important feature in the treatment of this disease. We have other invaluable methods which will never be given up, but whatever their value, rest at least in the beginning and more or less during the whole course of treatment is the most essential of them all, and though its application may undergo certain modifications it will always be our chief reliance even if a specific should be discovered."

It has been our practice during the past ten years to place all cases of minimal tuberculosis when first admitted to the hospital on strict bed-rest. A review of the exudative lesion group showed that the average length of time required for maximum resorption of the infiltrate was six months. We deviated from this routine when during the course of observation either a confirmed and persistent positive sputum or gastric lavage was obtained, or haemoptysis occurred, or roentgen evidence of extension of the disease or excavation was noted. In each of these instances, it is our opinion that there probably existed a cavity which could not be demonstrated by fluoroscopy and/or plain film. The importance of determining whether a cavity is present cannot be overemphasized. Such a finding would, of course, place the lesion in the moderately advanced stage of tuberculosis thus influencing the results of bed-rest alone. We are of the opinion that many of the relatively poor results obtained by some observers with so-called minimal lesions by bed-rest, and especially by those who reported a fairly high percentage of positive sputa in their cases, can be attributed to the fact that a significant number of their cases were really patients with small "hidden" cavities; and hence cases of moderately advanced tuberculosis. In certain instances by means of fluoroscopy in the oblique positions, antero-posterior films (instead of the conventional postero-anterior position, as most of these lesions are situated posteriorly and may be visualized more distinctly in the former view) or by means of laminography, we have been able to prove the presence of a cavity. In such cases, we always resort to pneumothorax and, if this is not available because of an obliterative pleuritis, to other forms as indicated.

CASE REPORTS

Case 1: G. Y., sixteen year old white female admitted to the Hudson County Tuberculosis Hospital on October 24, 1939. X-ray film on admission (plate 1) shows an exudative infiltrate between left apex and second anterior rib. The first five gastric lavages were negative on smear and culture and serial X-ray films showed slight resolution of the infiltrate with no evidence of any areas suspicious of cavitation. On March 4, 1940 a positive guinea pig report was obtained and was confirmed on a second gastric lavage on April 4, 1940. X-ray film on July 22, 1940 revealed a slight resolution of the infiltrate with no areas of excavation. Patient then was laminographed (plate 2) which showed a definite cavity, 1 cm. in diameter, underlying the anterior aspect of the first rib most

---

FIG. 1. Upper left. Case 1. G. Y. Admission X-ray, October 25, 1939, shows an exudative infiltrate in the left apex and first interspace.

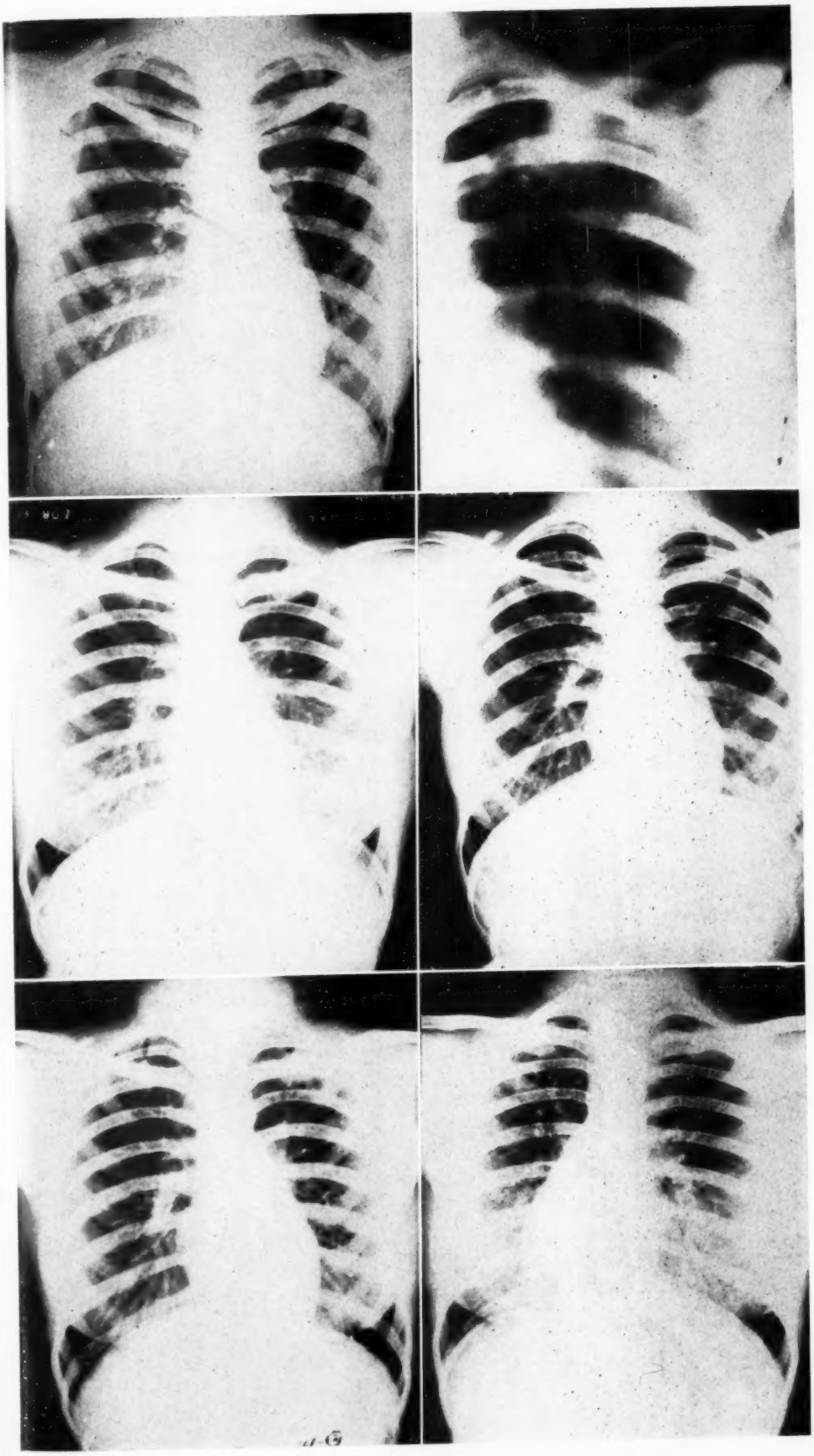
FIG. 2. Upper right. Case 1. G. Y. Laminogram at 4 cm. reveals definite cavity 1 cm. in diameter underlying the first left anterior rib. Routine postero-anterior chest film at this time revealed a residual productive infiltrate.

FIG. 3. Center left. Case 2. V. G. Admission X-ray revealed an exudate infiltrate in the left apex and second interspace.

FIG. 4. Center right. Case 2. V. G. Discharge film June, 1939 showed a residual productive infiltrate.

FIG. 5. Lower left. Case 2. V. G. X-ray, November 7, 1940, postero-anterior view, reveals an indefinite annular shadow in the left first interspace.

FIG. 6. Lower right. Case 2. V. G. Antero-posterior film of chest reveals definite cavity in left first interspace.



FIGS. 1–6

clearly visualized at the 4 cm. level. Pneumothorax was induced resulting in an effective collapse.

Case 2: V. G., sixteen year old white female, first admitted to the Hudson County Tuberculosis Hospital on November 7, 1938. X-ray film on admission (plate 3) showed an exudative patch of infiltrate in the left apex and second interspace. During her period of hospitalization 24 sputum examinations were done which were negative. She was kept on bed-rest until her discharge in June, 1939 at which time the X-ray film (plate 4) showed a residual productive infiltrate. She attended the clinic and remained asymptomatic. Serial X-ray films showed no change and her sputa remained negative. In November, 1940 she had a small haemoptysis. A postero-anterior X-ray film on November 7, 1940 (plate 5) showed an area suggesting cavitation while an antero-posterior film taken the same time (plate 6) unmistakably revealed a cavity in the first interspace 2 cm. in diameter. She was thereupon readmitted to the hospital, pneumothorax induced, with a resultant effective collapse.

From our studies to date, we have not had any reason to regret our policy of placing patients with active minimal lesions on a bed-rest regimen. By this procedure, we have effectively treated 78 per cent of these and thus saved them from the inherent complications that occur in any large group of pneumothorax patients. Of the 13 cases that showed progression, 12 were readmitted to our hospital. Pneumothorax was induced in 11 resulting in an effective collapse in all, while in one spontaneous control of the lesion was obtained by bed-rest after patient refused collapse therapy. As might well be expected, definitely poorer results were obtained in the patients with exudative lesions treated in the clinic, as evidenced by progression of disease in almost twice as many and 3 deaths as against none in the hospital treated group.

As to the care of patients with a controlled productive type of infiltrate, especially those that show a fibro-calcific type of lesion, we do not feel that hospitalization or even bed-rest is necessary. On the other hand, where there is a question as to the activity of the lesion and it is felt that the process is most probably productive, the patient should be put to bed, not necessarily in a hospital nor strictly in bed, but on a regimen which will call for several hours of rest during the day and for an early retiring hour. In either event, he must be observed every month by serial X-ray films in addition to careful sputum studies and his subsequent course will depend on these findings. Should this period of observation show the lesion to remain stationary and his sputa persistently negative, he must be impressed with the necessity for close observation under competent management for the remainder of his life.

We are well cognizant of the fact that all reinfection lesions have their inception as an exudative process of a greater or lesser extent. From our studies it is noted that most of these lesions show a tendency to clear leaving residual areas of productive infiltration. On the other hand, a small number do progress to tissue destruction and cavity formation. Because we are unable to ascertain which case will resorb and which will progress, we do not feel justified in collapsing every case of minimal tuberculosis. We agree with Amberson (17) that

it is hazardous in many cases to attempt to decide as to whether a particular lesion is active or arrested and only by means of serial X-rays films can this question be solved. Hence it must be unwise to collapse every minimal tuberculous lesion when first diagnosed as one will undoubtedly subject a number of patients with productive infiltrates, which will in the vast majority of instances do well, to a prolonged siege of unnecessary therapy. Those who practice immediate collapse therapy on minimal lesions must also occasionally collapse nontuberculous infiltrates for we do not rarely see patients with what appears to be a typical exudative infiltrate which will show complete resolution within a period of two or three weeks. The only way by which these nontuberculous infiltrates can be differentiated from a tuberculous lesion (in the absence of a positive sputum) is by serial X-ray study and this important differentiation cannot be made if the lung is collapsed. We also are in agreement with Eglee and Jones (18) who are of he opinion that the healing of tuberculous infiltration is not hastened by pneumothorax.

SUMMARY

1. One hundred and eighty-five cases of minimal tuberculosis, divided into those treated in the hospital and those managed in the clinic, are analyzed with reference to results and frequency of recurrences.

2. Bed-rest as an initial procedure is recommended in all instances of minimal exudative tuberculous lesions. Arrest of the disease by such treatment occurred in 78 per cent of our series.

3. Management of active disease in the clinic or at home is not as satisfactory as in the hospital or sanatorium, as evidenced by the fact that twice as many recurrences were encountered in the former group.

4. Collapse therapy is indicated in these patients only when progression of the lesion occurs, when positive sputa are recovered and fail to reverse after a liberal period of bed-rest or when haemoptysis is present.

5. When collapse became necessary in the hospital cases, a free pleural space was obtained in all but one instance weeks to months after admission.

SUMARIO

1. Analízanse, con referencia al resultado y a la frecuencia de las recurrencias, 185 casos de tuberculosis mínima, dividiéndolos entre los tratados en el hospital y los atendidos en la clínica.

2. En todo caso de lesiones tuberculosas exudativas mínimas recomiéndase el descanso en cama como procedimiento inicial, y con este tratamiento se estacionó la enfermedad en 78 por ciento de la serie.

3. El tratamiento de la enfermedad activa en la clínica o a domicilio no resulta tan satisfactorio como en el hospital o sanatorio, segun indica el haberse observado el doble de recurrencias en el primer grupo.

4. La colapsoterapia está indicada en estos enfermos únicamente cuando la lesión sigue avanzando, cuando el esputo resulta positivo y no se esteriliza después de un período largo de encamamiento, o cuando hay hemoptisis.

5. Cuando resultó necesario el colapso en los casos hospitalizados, se obtuvo un espacio pleural despejado, en todos los casos menos uno, de algunas semanas a meses después del ingreso.

REFERENCES

(1) KENDALL, W. B., AND ROSS, C. B.: Artificial pneumothorax after fourteen years, Am. Rev. Tuberc., 1929, *18*, 904.
(2) HEGNER, C. F.: Surgical rest in pulmonary tuberculosis, Ibid., 1928, *17*, 282.
(3) BRAUER, M. J.: The treatment of the "early" case of tuberculosis, Ibid., 1930, *22*, 57.
(4) CRAIG, F. A.: The field of pneumothorax in the treatment of tuberculosis, Internat. Clinics, Vol. 1, Series 48, 1938.
(5) RINGER, P. H.: Sees abuse of collapse therapy, N.T.A. Bull., October, 1940, *26*, 147.
(6) POTTER, B. P.: Modern concepts on the collapse therapy of tuberculous pulmonary cavities, Am. Rev. Tuberc., 1935, *31*, 499.
(7) HAYES, J. N.: Views various phases of treatment, N.T.A. Bull., August, 1940, *26*, 117.
(8) AMBERSON, J. B., JR.: Clinical studies of the healing of pulmonary tuberculosis, The absorption of pulmonary deposits, Am. Rev. Tuberc., 1924, *10*, 227.
(9) BAUM, F.: The logic of collapse therapy, J. Thoracic Surg., 1940, *9*, 322.
(10) WEBB, G. B.: The early diagnosis and early care of pulmonary tuberculosis, J. A. M. A., 1929, *92*, 1811.
(11) GROSS, M., AND ENGLISH, S. B.: The treatment of the child with the adult type of active pulmonary tuberculosis: A plea for compression therapy, Am. Rev. Tuberc., 1937, *35*, 303.
(12) MYERS, J. A.: Artificial pneumothorax with particular reference to the ambulatory patient, J. Thoracic Surg., 1937, *6*, 513.
(13) O'BRIEN, E. J.: The indications for the surgical treatment of pulmonary tuberculosis, Am. Rev. Tuberc., 1929, *20*, 787.
(14) O'BRIEN, E. J.: The choice of procedure in collapse therapy, J. Thoracic Surg., 1935, *5*, 123.
(15) TURNER, G. C., AND COLLINS, L. L.: The feasibility of artificial pneumothorax in minimal cases of tuberculosis, Am. Rev. Tuberc., 1936, *34*, 792.
(16) MINOR, C. L.: The evolution of the modern treatment of pulmonary tuberculosis, Ibid., 1929, *18*, 794.
(17) AMBERSON, J. B., JR.: The significance of roentgenographic mutations of the lesions of chronic pulmonary tuberculosis, Ibid., 1923, *6*, 591.
(18) EGLEE, E. P., AND JONES, O. R.: A review of one hundred re-expanded cases of artificial pneumothorax, Ibid., 1937, *35*, 500.

PLEURISY WITH EFFUSION[1]

J. L. BONILLA, JR.[2]

The object of this investigation was a study of the course and prognosis of tuberculous pleurisy with effusion. The results obtained were compared with those of previous studies (1) in Rosario, Argentina, where epidemiological conditions are quite different from those in the United States. The possibility that types of tuberculosis clinically identical might exhibit differences in evolution, attributable to epidemiological factors, was the source of inspiration of the study. Unfortunately the previous experience mentioned was based solely on clinical criteria in a division for respiratory disease attached to a department of clinical medicine, where the lack of social service made continued and accurate observation of patients difficult. The investigation here reported was quite different in that adequate observation was accorded each case, providing accurate medical and social information not obtainable in the earlier study. Comparison of the experience in the two countries has been possible, accordingly, only in a few respects, and in this report attention will be given chiefly to observations made in Philadelphia.

The records were studied of approximately 2,000 families in which there had occurred at least one case of presumed tuberculosis, including pleurisy with effusion. Seventy-nine instances of pleurisy with effusion were collected, excluding patients who were known previously to have had reinfection-type tuberculosis.

The ages of the patients studied in the report here submitted were as follows: eight to eleven years, 9 cases; twelve to twenty years, 17 cases; twenty-one to thirty years, 24 cases; thirty-one to forty years, 19 cases; more than forty years, 10 cases. The oldest patient was sixty-four years of age. Forty-nine patients were males and 30 were females. Twenty-two were white and 57 were Negroes. The group of 9 young children is given separate consideration. The adult group has been divided into two subgroups according to the presence or absence of radiologically evident pulmonary infiltration at the time of diagnosis of the pleurisy; in 30 patients infiltration was evident and in 40 it could not be detected.

FATE OF PATIENTS WITH PLEURISY WITH EFFUSION

The results of observation are indicated in table 1. In the group of adults without infiltration at the time of pleurisy certain differences between whites and Negroes were exhibited. The former subsequently developed radiological evidence of infiltration more frequently (in 54.5 as compared with 37.9 per cent of cases), but in only one white patient of this group did clinical symptoms of tuberculosis appear and no death occurred; 91 per cent of the group were clini-

[1] From the Henry Phipps Institute, University of Pennsylvania, Philadelphia, Pennsylvania.

[2] Fellow of The Division of Medical Sciences of the Rockefeller Foundation.

cally well at the end of the period of observation. In contrast, in the 11 Negro patients who developed radiological signs of tuberculosis after the appearance of the pleurisy, 8 showed progression with clinical manifestations and 6 died of their disease. These differences in evolution suggest a variation in resistance in the two racial groups, but it is noteworthy that these differences were not found in the group that already had pulmonary infiltration at the time of the pleural involvement. In this group the figures for development of clinical tuberculosis and for deaths correspond closely in the two races.

TABLE 1

Fate of patients with pleurisy with effusion

PULMONARY CONDITION AT TIME OF DIAGNOSIS OF PLEURISY	NUMBER OF PATIENTS		SUBSEQUENTLY DEVELOPED X-RAY EVIDENCE OF INFILTRATION	SUBSEQUENTLY DEVELOPED CLINICAL TUBERCULOSIS WITH SYMPTOMS	DEATHS FROM TUBERCULOSIS	REMAINED CLINICALLY WELL
Parenchymal infiltration absent	White	11	6 (54.5%)	1 (10.5%)	0	10 (91.0%)
	Negro	29	11 (37.9%)	8 (27.6%)	6 (20.7%)	21 (72.4%)
Parenchymal infiltration present	White	9		6 (66.6%)	4 (44.5%)	3 (33.3%)
	Negro	21		13 (62.0%)	7 (33.3%)	8*(38.0%)

* One death from carcinoma of stomach.

TABLE 2

Results of treatment of 69 adults with pleurisy with effusion

INFILTRATION AT TIME OF DIAGNOSIS	TREATMENT	NUMBER OF PATIENTS	SUBSEQUENTLY DEVELOPED CLINICAL TUBERCULOSIS	DIED OF TUBERCULOSIS	REMAINED CLINICALLY WELL
Absent (mean interval of observation 31.9 months)	Rest	15	3 (20%)	2 (13%)	12 (80%)
	Ambulatory pneumothorax	4	1 (25%)	1 (25%)	3 (75%)
	None	20	4 (20%)	2 (10%)	16 (80%)
Present (mean interval of observation 36.2 months)	Rest	7	5 (71%)	0	2 (29%)
	Ambulatory pneumothorax	10	7 (70%)	5 (50%)	3 (30%)
	None	13	7 (54%)	6 (46%)	6 (46%)

In the group originally without infiltration the pulmonary infiltration developed in the whites on the average thirty-eight months, and in the Negroes 21.3 months after the pleurisy. Clinical symptoms began in Negroes twenty-six months after the pleurisy, and in the single case where symptoms occurred in whites, this occurred after nineteen months.

RELATION TO TREATMENT

Comparison of the evolution of disease in the different groups has been studied according to the type of treatment taken. Patients have been classified for this

purpose in 3 groups: (*1*) patients on bed-rest for at least four months in home, hospital or sanatorium, (*2*) ambulant patients treated by pneumothorax, and (*3*) patients who refused treatment. No racial difference in response to treatment was detected; accordingly the results in Negro and white patients are combined in table 2. As can be seen, the influence of treatment appears slight in patients with pleurisy alone. No significant differences are observed in the three categories; it was as if the future development of pulmonary tuberculosis and its outcome depended more upon individual factors than upon the type of treatment. On the other hand, in patients who had pulmonary infiltrations at the time of onset of the pleurisy the response was very different. Among patients who took rest treatment clinical tuberculosis developed as frequently as in the other two groups, but the evolution of the disease was much more favorable, for no patient died, while of those taking no treatment or only ambulatory pneumothorax treatment, almost 50 per cent died.

CHARACTER OF INFILTRATION

The following tabulation indicates the localization of the infiltration as related to the side of the thorax in which pleurisy had occurred.

	HOMO-LATERAL	CONTRA-LATERAL	BILATERAL	HILUM ENLARGEMENT
Infiltration at time of pleurisy	15	4	9 (1 miliary)	2
Infiltration after pleurisy	7	4	6 (2 miliary)	

The table shows that the infiltrations do not develop solely on the side in which the effusion occurred, as certain authors, for example, Kallner (2) and Schneider (3), have reported. Actually the infiltration was frequently bilateral or confined to the side opposite to that of occurrence of the pleurisy, a fact which favors the view of haematogenous origin of the infiltration.

In 7 patients a haematogenous pathogenesis appeared corroborated by the presence of extrathoracic tuberculosis. One white patient developed epididymitis, symptomatically evident three years after the pleurisy; generalization and death followed. The remaining instances of extrathoracic tuberculosis occurred among the Negro patients. There were 2 fatal cases of generalized miliary tuberculosis, occurring eleven and seventeen months respectively after the pleurisy. One patient died of meningitis eleven months and another of peritonitis five months after pleurisy. In 2 cases, one with a rectal abscess and the other with cervical adenitis, the outcome was favorable.

Bilateral pleural effusion occurred in 2 white patients and in one Negro patient. One of the whites died of a nontuberculous illness and another had a benign course with no pulmonary sequelae. The Negro developed infiltration with clinical symptoms.

PRESENCE OF TUBERCLE BACILLI IN PLEURAL FLUID

The results of guinea pig inoculation of the pleural exudate were available in 34 patients, as shown in the following:

	POSITIVE	DEVELOPED INFILTRATION	NEGATIVE	DEVELOPED INFILTRATION
Cases without infiltration....	7	2 (2 died)	15	7 (1 died, 2 sick, 4 well)
Cases with infiltration.....	7 (4 died, 2 sick, 1 well)		5 (2 died, 1 sick, 2 well)	

It is evident that while a positive result can serve to establish the diagnosis of tuberculous pleurisy, a negative result cannot rule out this diagnosis. As to its significance as a prognostic sign, the prognosis seems to be somewhat worse in cases with positive results, which accords with the evidence of other authors, including Gaarde (4), Arborelius (5) and Silberschmidt (6).

PLEURISY IN CHILDREN

Nine cases of pleurisy were observed in children eight to eleven years old, 7 of them in Negroes and 2 in whites. The children of the series were examined as contacts and all except 2 had X-ray films prior to the pleurisy and with one exception previous tuberculin tests. In spite of the small number of cases some interesting facts were learned from both methods of examination in the course of observation. Of the 7 cases with previous X-ray examination, the latter was negative in 6 cases at the time of the first examination, and the average interval in months between the negative X-ray and the observation of pleurisy was 7.6 months. On one occasion primary infiltration was observed at the first examination and two months later pleurisy supervened on the same side. Disability resulted from the pleurisy in the 6 primary cases only infrequently. In one case pulmonary infiltration was observed; in this case it was on the same side, without modification of the size of the hilum lymph nodes. In the 5 other cases there was no pulmonary abnormality. The radiographic image in the 2 cases without previous examination showed in both an increase in size of the hilum nodes, one on the same side as the pleurisy and the other on the opposite side.

The tuberculin reaction was studied prior to the development of the effusion in 6 cases. In one instance the test was made only at the first examination. In this case the result was negative. The pleurisy developed nine months later. In 4 cases the reaction was positive at the time of first examination. The average interval between the test and the occurrence of pleurisy in these cases was six months. In the other case the reaction changed from negative to positive during the period of observation; the pleurisy developed three months after the positive reaction was noted.

We have compared these observations in children with those in a group of 13 adults composed of 9 Negro and 4 white patients who were tested with tuberculin prior to the development of pleurisy. Tuberculin tests were made once only in 3 cases, with negative result, the pleurisy appearing on the average twenty-four months later.

In 7 cases the reaction was positive at the first examination. The pleurisy made its appearance after an interval on the average of thirty-two months. In the remaining 3 cases the patients became allergic during the course of observa-

tion, the pleurisy becoming evident an average of eight months after first observance of a positive reaction.

In 2 of the cases with previous roentgenological study, hilar adenopathy had been demonstrated respectively ten months and two years before the pleurisy. In the other 9 cases the examination was negative; as stated at the outset all those cases with previous roentgenological evidence of reinfection tuberculosis were excluded.

It will be seen that in many of the cases, both in the group of children and in the adults, the pleurisy could not be considered a direct result of the first infection, since it was separated by a period of time which was often very long. This phenomenon has been noted by Wallgren (7), who stated in addition that it is impossible to foresee and take measures to prevent the occurrence of pleurisy in any tuberculin-positive child. The observations in this study support this view as respects adults.

The outcome of pleurisy in children as observed in this study was as follows. In one case pneumothorax was induced, and five years later the patient was well, without having developed pulmonary tuberculosis. In the other 8 there was no treatment. Five patients progressed favorably and 3 developed tuberculosis of the reinfection type, 2 of them dying from progression of their lesions. In the 2 fatal cases the pleurisy appeared at the ages of nine and eleven years respectively. In the former, death occurred ten years later and in the other, two years later. The presence of pulmonary infiltration or hilar adenopathy did not seem to have a bearing on the subsequent course in any case; of those who died, one had a primary complex at the time of development of the pleurisy while in the other there was no visible pulmonary or lymph node lesion.

CONTACT

Among the 70 adults, definite exposure to a patient with positive sputum, usually in the same family, was found in 23 cases (9 whites and 14 Negroes). In 8 of these the contact continued after the appearance of the pleurisy; in the other 15 it was discontinued when the pleurisy was discovered.

The prognosis was apparently not affected by the presence or absence of contact, for the outcome was favorable in 6 of the patients whose exposure to tuberculosis continued. We had observed in Argentina that more serious developments occurred when contact was continued after the production of pleurisy.

COMMENT

The number of cases of pleurisy with effusion found in the records of the Henry Phipps Institute was much below expectation. To determine whether this corresponded with the general incidence of pleurisy with effusion in Philadelphia, data were obtained from the Philadelphia General Hospital. During the period 1936–1940, a total of 123,748 patients were admitted. The number of patients diagnosed as having pulmonary tuberculosis was 5,617; the number with pleurisy with effusion was 287. This figure appears extraordinarily low in

comparison with the Argentina experience. It is possible that the relative infrequency of pleurisy with effusion in Philadelphia is a reflection of the general decline in nonpulmonary tuberculosis in the United States, as Thompson (8) has suggested might be the case in scrofula.

The difference in evolution of pleurisy with effusion in white and Negro patients is of considerable interest. In patients who had pulmonary infiltration at the time of the pleurisy the prognosis was almost equally poor in the two races. On the other hand, white patients who had no infiltrations rarely developed clinical tuberculosis, while among the Negro patients the development of fatal tuberculosis was not uncommon. There is a striking similarity between these observations and Brailey's observations on the results of tuberculous infection in infancy. Brailey (9) has found that the likelihood of a fatal outcome was almost equal in white and Negro infants who had pulmonary lesions. Among infected infants who did not have pulmonary infiltrations, there was a marked racial difference. White infants rarely developed serious tuberculosis subsequently, while fatal tuberculosis developed not infrequently in the Negro infants of this group.

Evidence has been presented in this report that the pulmonary lesions which were present at the time of the pleurisy or which developed later, were often the result of haematogenous dissemination. It is possible also that the pleurisies were of haematogenous origin. The thoracoscopic investigations of Jacobaeus and Unverricht showed the possibility of haematogenous seeding of the pleura by their finding of isolated tubercles in the parietal pleura in cases of serofibrinous exudation without abnormal pulmonary shadows (10), and our own investigations (1) as well as those of Gad (11) have shown that it is possible to obtain a high percentage of positive gastric washings in patients with pleurisy, without concomitant demonstrable lesions of the lung. It is obvious that the origin of these bacilli could be in small subpleural lesions which would give rise also to the effusion and later disappear, but it is also possible that they could be due to small haematogenous foci not visible radiologically at the time of the pleurisy, and which might be manifested later.

SUMMARY

1. Of the various factors determining the fate of those developing pleurisy with effusion, the most important is whether or not pulmonary infiltration is present at the time of development of the pleurisy. If there is no infiltration the course seems to depend principally on individual factors, There is a great difference between the white and Negro races. When infiltration coexists with the pleurisy this fact surpasses in importance the racial factor and the course is related in great measure to the nature of the treatment received. When bed-rest was taken for a sufficient time, that is, at least four months, the late results were much more favorable than when no treatment was taken or when pneumothorax was administered without bed-rest.

2. The large number of instances in which the infiltration was bilateral or

localized on the side opposite to the effusion, especially when it appeared after the pleurisy, suggests that in many cases the origin of the infiltration is by way of the blood stream.

3. Study of a small group of children with pleurisy with effusion who had prior tuberculin tests and a group of 13 adults who had tuberculin tests previous to the pleurisy suggests that pleurisy with effusion is a phenomenon without direct relation to primary infection.

SUMARIO

1. De los varios factores que determinan la evolución de los enfermos que manifiestan pleuresía con derrame, el más importante es la existencia o falta de infiltración pulmonar al presentarse la pleuresía. Si no la hay, la evolución parece depender principalmente de ciertos factores fundamentales. Por ejemplo, obsérvase una gran diferencia entre las razas blanca y negra. Cuando la infiltración coexiste con la pleuresía, ésta sobrepuja en importancia el factor étnico y la evolución se relaciona en gran parte con la naturaleza del tratamiento administrado. Cuando el descanso en cama duró tiempo suficiente, es decir, por lo menos cuatro meses, los resultados tardíos fueron mucho más favorables que cuando no se recibía tratamiento o se empleaba el neumotórax sin encamamiento.

2. El gran número de casos en que la infiltración era bilateral o estaba localizada en el lado opuesto al derrame, en particular cuando se presentó después de la pleuresía, indica que en muchos casos la infiltración tiene lugar por vía circulatoria.

3. El estudio de un pequeño grupo de niños que padecían de pleuresía con derrame, en los que se habían realizado antes reacciones a la tuberculina, y un grupo de 13 adultos en los que se hicieron reacciones antes de la pleuresía, indica que la pleuresía con derrame es un fenómeno que no guarda relación directa con la infección primaria.

I wish to express my thanks to Drs. Esmond R. Long and Harold L. Israel for their advice in the prosecution of the studies here described and the preparation of this article.

REFERENCES

(1) Bonilla, J. L., Jr.: Las pleuresias serofibrinosas del adulto, Revista méd. de Rosario, 1938, *28*, 1.

(2) Kallner, S. K.: On the prognosis of exudative pleurisy, Acta med. Scandinav., 1937, *92*, 549.

(3) Schneider, L.: Pulmonary tuberculosis following sero-fibrinous pleurisy, Brit. J. Tuberc., 1939, *33*, 96.

(4) Gaarde, F. W.: The prognosis of pleurisy with effusion, J. A. M. A., 1930, *95*, 249.

(5) Arborelius, M.: Klinische Studien über die Tuberkulose-infektion bei Erwachsenen, besonders mit Hinsicht auf das Vorkommen von Primärinfektionen., Svenska läk.-sällsk. handl., 1930, *56*, 115.

(6) Silberschmidt, P.: Zur Prognose und tuberkulösen Aetiologie der serösen Pleuritis, Beitr. z. Klin. d. Tuberk., 1925, *60*, 128.

(7) WALLGREN, A.: Pathogenesis of acute serofibrinous pleurisy, Am. J. Dis. Child., 1929, *38*, 829.

(8) THOMPSON, B. C.: Tuberculosis of cervical lymph nodes; incidence of its manifest, latent and obsolete forms in 6,000 dispensary patients, Am. Rev. Tuberc., 1938, *37*, 410.

(9) BRAILEY, M.: Mortality in tuberculin-positive infants, Bull. Johns Hopkins Hosp., 1936, *59*, 1.

(10) Citation by FREDERIKSEN, J. A.: Studien über Pleuritis exsudativa, Ergebn. d. ges. Tuberk., 1934, *6*, 619.

(11) GAD, U.: On the diagnostic value of gastric lavage in adult patients without roentgenographic foci in the lungs, Acta tuberc. Scandinav., 1937, *11*, 189.

AMBULATORY PNEUMOTHORAX[1, 2]

Some Interesting Experiences Encountered over a Period of Ten Years in a Teaching University Clinic

H. I. SPECTOR AND H. E. OPPENHEIMER

Much has been written about pneumothorax, but comparatively little is found in the literature about the results obtained with ambulatory pneumothorax treatments and still less regarding the medical and social complications arising during the course of ambulatory pneumothorax treatments.

It occurred to the writers that the experiences encountered and the results obtained in a University Teaching Clinic over a period of ten years, where different physicians have given the treatments to the same patients, might be of interest.

In order to shorten the stay of the pneumothorax patients at the University Sanatorium, Mt. St. Rose, an ambulatory pneumothorax clinic was opened at one of the St. Louis University hospitals on November 1, 1930, which is still in existence. This University pneumothorax clinic is one of the oldest clinics in this section of the country. During these ten years, cases referred for treatment were mainly from Mt. St. Rose, but patients from other sanatoria and hospitals were accepted for refill treatments. An initial pneumothorax was never attempted in this out-patient clinic because, though we believe that it may be justifiable for public health reasons, it is not an ideal way of starting pneumothorax treatments. Furthermore, we contend that, with few exceptions, it is too dangerous a procedure to try in an ambulatory clinic. In emergencies, patients were given the initial treatment in the hospital proper and then continued in the out-patient department.

Briefly, the general routine was as follows: Every new patient referred to us for treatment was given a complete examination in the chest clinic. The frequency of refills and the amount of air given was then decided upon. With a few exceptions, the principle of low tension pneumothorax was used for we maintain that this procedure is the safer one. All patients were kept at partial bed-rest at first; exercise was gradually increased until they were able to do part-time work. Patients were encouraged to go to the Occupational Work Shop for part-time work, since such type of follow-up therapy is very helpful in the economic rehabilitation of the patient (1, 2).

As has already been described in a previous publication by one of us (3), the duration of pneumothorax treatments depended somewhat on the type and character of the existing disease before pneumothorax was instituted. In brief, exudative unilateral disease was kept collapsed a shorter period, usually three years, while patients with previously caseo-pneumonic tuberculosis with or without cavitation were kept collapsed at least five years.

[1] From the Department of Internal Medicine, Chest Division, St. Louis University and the Firmin Desloge Hospital, St. Louis, Missouri.

[2] Read before the Faculty Seminar, St. Louis University, March 27, 1941.

Before permitting reëxpansion of a lung, certain requirements were necessary, such as freedom of symptoms, repeated negative sputa for at least a year, a normal Schilling count, stationary physical signs, a maintenance of weight and the ability to do either partial or full-time work.

Reëxpansion of a lung was accomplished in three ways, either by increasing the time interval between refills, decreasing the amounts at the regular intervals or both. As the lung reëxpanded and came close to the chest walls, roentgenograms were taken and together with the bacteriological and stethoscopic findings were studied for possible reopening of cavities or other evidence of active disease. In most reëxpanded cases a serous fluid developed because of the increase in the negative pressure. In some cases a shifting of the mediastinum to the pneumothorax side took place. In some instances relapses occurred, but it should be

TABLE 1

End-results of "reëxpanded cases"

Total number reëxpanded				21
By choice	17	Tuberculous	12	9 are well: 7 years 1; 6 years 1; 5 years 4; 1 year 1; 2 years 1; 6 months 1
				2 relapsed in opposite lung
				1 Recollapsed because of massive effusion on reëxpanded side—well and working three years
		Nontuberculous	5	3 dead
				2 living
Obliterative	4	Well and working		5 years 1; 3 years 1; 2 years 2

remembered the patients served were in the very low economic bracket which might be the explanation in part for these relapses.

In addition to making it possible for an earlier discharge of patients from the University Sanatorium, Mt. St. Rose, this small clinic served to train twenty resident physicians in the principles and practices of pneumothorax treatments, each physician receiving six months training, and medical students, junior internes and nurses being the spectators.

The many interesting experiences and complications, physical and socio-economic, encountered during the ten-year period from November 1, 1930 to November 1, 1940, as well as the effectiveness of ambulant pneumothorax treatment from the viewpoint of rehabilitation follows:

This study covers 101 cases, all white, 5 of which were nontuberculous. There were 61 females and 40 males in age groups varying from fifteen to fifty-four, the majority (69 per cent) falling in the age group fifteen to twenty-nine. The tuberculous cases were both in the moderately advanced or far advanced group.

No minimal cases were included. Most of the cases had unilateral disease. In the group of 96 tuberculous patients there were 10 with bilateral disease, 8 of whom were given pneumoperitoneum refills and 2 bilateral pneumothorax treatments simultaneously.

TABLE 2

Complications during treatment

Medical

- Spontaneous pneumothorax incidental to treatment 5
  - Mixed empyema 2
    - Died later 1
    - Recovered 1
  - Serous effusion with recovery 3
- Pneumonia in opposite lung with recovery 1
- Acute appendicitis with recovery ..... 2 (1 in bilateral pneumothorax case)
- Seasonal bronchial asthma developing during treatment 3
- Chancre of tonsil 1
- Atelectasis of uncollapsed lung with recovery 1
- Air embolus in seven months pregnant woman with recovery 1
- Broken needle 1
- Some mediastinal herniae and effusions were present when patients came to clinic—a few developed in the clinic during period of treatment

Social

- Some engagements
- Some broken engagements
- Some marriages
- Some divorces
- Pregnancies ..... 5 in 3 patients
  - Twice in 2 patients during period of pneumothorax treatment
  - Once in 1 patient—following reëxpansion—twins with no ill effects

TABLE 3

Comparison of major complications

	NUMBER OF PATIENTS	NUMBER OF TREATMENTS	AIR EMBOLI	RATIO OF AIR EMBOLI TO NUMBER OF REFILLS	DEATHS	EMPYEMA			SPONTANEOUS PNEUMOTHORAX	PLEURAL SHOCK
						Number	Ratio of empyema to number of refills	Dead		
St. Louis University Clinic	101	4,692	1	1 in 4,692	0	2 (1 in lung abscess)	1 in 2,346	1	5	0
Chicago Municipal Tuberculosis Clinic	2,366	83,245	28	1 in 2,973	8	25	1 in 2,349	12	3	1

A total of 4,692 treatments were given by twenty physicians, 186 of which were pneumoperitoneum refills. The greatest number of pneumothoraces given to a single patient with complete reëxpansion was 197 over a period of seventy-four months.

A total of fifty pneumothorax refills were given to five nontuberculous cases mainly to control haemorrhage resulting either from bronchiectasis, lung abscess, mediastinal cysts or lymphosarcoma. While the immediate objective of controlling haemorrhage was achieved, ultimately the treatments had to be discontinued because they were ineffective in controlling the disease.

The status of the 101 patients at the end of ten years was as follows: 38 were still under treatment in the clinic; 26 relapsed and were sent back to the sanatorium and of these, 12 died later; in 21 the lungs were reëxpanded; the condition of 13 was not known; and 3 were under the care of private physicians and apparently well. The end results of "reëxpanded cases" are seen in table 1.

As far as economic rehabilitation is concerned, 45 were working full time sometime during pneumothorax treatment, 9 part time, 39 were not working and 8 could not be classified.

The medical as well as the social complications that occurred during treatment as well as a comparison of the major complications with those of the Chicago Municipal Tuberculosis Clinic are seen in tables 2 and 3, respectively.

CONCLUSION

From data presented, it seems justifiable to state that pneumothorax refills in the ambulant patient are fairly safe and effective in pulmonary tuberculosis. The rather high percentage of spontaneous pneumothoraces incidental to the treatments is expected under the circumstances and needs no further explanation. The relapses that occurred in many instances can be explained on the social and economic basis, since many of the patients were financially assisted by the local social agencies.

Ambulatory pneumothorax clinics are worth while adjuncts to the teaching of tuberculosis to the medical students and resident staff of a university hospital.

CONCLUSIONES

Por los datos presentados, parece justificado declarar que los rellenos del neumotórax en los enfermos ambulantes son bastante seguros y eficaces en la tuberculosis pulmonar. El porcentaje algo elevado de neumotórax espontáneo inherente al tratamiento es de esperar dadas las circunstancias, y no necesita más explicación. Las muchas recidivas observadas pueden explicarse sobre una base social y económica, puesto que muchos de los enfermos eran socorridos económicamente por los organismos de obras sociales de la localidad.

Las clínicas de neumotórax ambulante son accesorios meritorios de la enseñanza de la tuberculosis a los estudiantes de medicina y claustro residente de un hospital universitario.

The writers wish to acknowledge with thanks the coöperation given them in this work by Dr. G. O. Broun, Director, Out-Patient Department, Firmin Desloge Hospital, and by Sister M. Anita.

REFERENCES

(1) SPECTOR, H. I.: In what way does occupational therapy assist in the recovery from tuberculosis, J. Occupational Therapy & Rehabilitation, 1936, *15*, 41.

(2) SPECTOR, H. I.: Employment for the ex-tuberculous patient, Am. Hosp. A., 1935, *37*, 376.

(3) SPECTOR, H. I.: When therapeutic pneumothorax for tuberculosis should be instituted and when it should be discontinued, J. Missouri State Med. Soc., January, 1937, p. 9.

(4) TICE, F., AND HRUBY, A.: Collapse therapy at the Chicago Municipal Tuberculosis Sanitorium, Bull. City of Chicago Municipal Tuberc. San., 15–16–17, Years 1935–1936, p. 114.

CONTRALATERAL PNEUMOTHORAX

M. LUCACER[1]

Exactly ten years ago I reported in this REVIEW the immediate results of primary contralateral pneumothorax (1).

Ascoli (2) defines the term primary contralateral pneumothorax as a pneumothorax applied on the healthy side when pneumothorax on the diseased side can not be carried out because of pleural obliteration.

The rationale of the primary contralateral pneumothorax is the well known, usually favorable contralateral effect of a pneumothorax if performed with subatmospheric pressure. This beneficial effect is attested to by a large clinical experience. There is frequently an interdependence of the pressures existing in both pleural cavities so that variations of pressure in one cavity (for example, by introduction of air) also cause variations of pressure in the other cavity (Bordet and Parodi (3), Lucacer and Polizzotto (4), Schill (5)). The result is a lowering of the bilateral intrapleural pressure with a diminution of the elastic tension of the pulmonary parenchyma bilaterally. If the unilateral pneumothorax is performed with subatmospheric pressures the contralateral lung does not undergo vicarious hyperventilation. In contrast to positive-pressure, compressive pneumothorax in subatmospheric pneumothorax the volume and mobility of the contralateral lung are diminished (Epifanio (6)).

Ascoli and I believe that the transmission of the variations in the intrapleural pressure from one side to the other is brought about principally by the mediastinum which becomes displaced toward the opposite side. Parodi (7) believes that the transmission of the variations in pressure takes place through the bronchial system.

The paramount fact, however, is that the well established contralateral effect of pneumothorax can be achieved by means of a primary contralateral pneumothorax when a homolateral pneumothorax is impossible. Naturally such a contralateral pneumothorax will be less effective than a homolateral one. It is well known that in a homolateral pneumothorax the effect on the contralateral lung will be much smaller than that on the directly treated lung.

The indications for the primary contralateral pneumothorax are restricted. To-day they appear even more restricted than ten years ago. The reason is the surprising development of pulmonary surgery in the last decade. Furthermore, because of improved knowledge of pulmonary physiomechanics, the size of the thoracoplasties have been reduced to a minimum-optimum (partial thoracoplasty). To-day, in the majority of cases, there is no longer any substantial disagreement as to the proper therapeutic measures to be used. Thus, if a case of clinical disease is not amenable to recovery after a reasonable period of sanatorium care, a pneumothorax will be tried; if this is impossible (or was ineffective after section of adhesions) a thoracoplasty strictly limited to the extent of the

[1] 887 Union Street, Brooklyn, New York.

lesions has to be performed. Extrapleural pneumothorax and intracavitary aspiration may divert only a limited number of cases from the outlined pattern. In a few particular cases a limited thoracoplasty may be a more rapid solution than the pneumothorax.

Can the primary contralateral pneumothorax substitute the homolateral pneumothorax when the latter is impossible or has been ineffective?

The answer is that only in a limited number of cases such a substitution will be completely successful. These are cases of recent, moderately advanced, mostly exudative lesions, localized in the upper lobe and in which the mediastinum, especially its superior portion, will be dislocated to a great extent; but the last condition is not an obligatory prerequisite to success. In the majority of cases however the primary contralateral pneumothorax will bring about a disappearance of symptoms even if severe, a remarkable improvement of the general condition of the patient and a greater or smaller clearing of the lesions; the exudative part of the lesions will disappear; there will be a trend to fibrosis and existing cavities will become smaller. The practical effect is that thoracoplasty, if still required can be more limited (one to two and even three ribs, sometimes, may be spared from being resected). The patient will be in better general condition for the thoracoplasty.

Further, there is another field for application of a primary contralateral pneumothorax which is the following: in cases in which lesions on one side require a thoracoplasty, but the integrity of the other side is questionable, a primary contralateral pneumothorax of short duration will solve the problem. In the majority of cases the "doubtful" side will be stabilized and the extent of the thoracoplasty will be reduced. Finally some authors (Gwerder-Pedojia (8), Fiori (9), Pons (10)) claim successful results with a primary contralateral pneumothorax in cases of severe haemoptysis in which a homolateral pneumothorax was impossible and the common means of treatment had failed.

A primary contralateral pneumothorax is to be maintained with strictly subatmospheric pressures. From radiokymographic and ergomanometric studies I and Lo Monaco (11) have shown that the costal movements on both sides are equal and minimal when the pressure in the pneumothorax remains from -4 to -2 in inspiration and from $+1$ to $+2$ in expiration.

In the primary contralateral pneumothorax there are no particular risks or complications but those of a homolateral pneumothorax. Pleural effusions are of the same frequency as in homolateral pneumothorax and are usually small. Adhesions, if found, can only be sectioned if the volume of the air pocket is temporarily enlarged.

The results of the application of the primary contralateral pneumothorax reported in the literature thus far cannot be accurately appraised, because of the divergent material used at the various clinics. For reason of brevity, I shall not present single case reports but rather summaries of series of cases.

Ascoli and I (12) performed a primary contralateral pneumothorax indiscriminately in all cases in which a homolateral pneumothorax was impossible.

We summarized the results of 18 cases treated over a period of three years as follows:

1: Slow, but progressive improvements identical to those which a unilateral pneumothorax in cases with bilateral lesions has on the opposite lung. This was observed in 10 cases.
2: Rapid and progressive improvements identical with those observed in homolateral pneumothorax. Noted in 3 cases.
3: No improvement at all was observed in 5 cases.

Fici (13) reports 11 cases. His cases were those in which surgical treatment was considered impossible or was refused by the patient. However, even with these obviously unfavorable cases he obtained one "healing," 4 "definite improvements," 1 "doubtful result" and "no appreciable results" in 5 cases.

Better results were reported by Malpeli (14) in more carefully selected cases. Here is the author's own summary:

Cases treated: 22

Afebrile after 6 months	16	72.72%
Afebrile after 12 months	2	9.09%
Gained weight	17	77.27%
Lost weight	5	22.73%
Pleural effusions	3	13.63%
Were Koch-positive initially	20	90.90%
Remained Koch-positive after 6 months	11	50.00%

The most striking results were reported by Tobè and his associates (15). They restricted the indications to well selected cases and applied the primary contralateral pneumothorax only with the purpose of reducing the extent of the subsequent thoracoplasty.

They treated 18 cases in which 12 showed great improvement as follows:

1: In 2 cases the improvement was so remarkable that thoracoplasty was later found unnecessary.
2: In 3 cases the progress also pointed to a possible avoidance of thoracoplasty.
3: In 7 cases only a subsequent limited thoracoplasty (maximally of five ribs) was found necessary. Of these, 4 cases had excellent results.
4: In 5 cases with old inert lesions the results were poor.

In several countries many other authors have reported on the primary contralateral pneumothorax to: Italy (16 to 25), France (26 to 32), Argentine (32 to 34), Brasil (35), Austria (36) and Germany (37).

It is an interesting commentary that no attempts, as far as I could determine, of primary contralateral pneumothorax have been made in this country. It appears to me that the value of the primary contralateral pneumothorax deserves to be drawn to the attention of the American physician as it has, I believe, demonstrated a limited though useful application in the field of pulmonary tuberculosis.

SUMMARY

The literature on contralateral pneumothorax is briefly reviewed. On the basis of the author's own observations and the results published, it is suggested that contralateral pneumothorax is beneficial in a small percentage of well chosen patients with pulmonary tuberculosis. The narrow field of indications is defined.

SUMARIO

Repásase sucintamente la literatura relativa al neumotórax contralateral. Tomando por base las propias observaciones del autor y los resultados publicados, indícase que el neumotórax contralateral resulta beneficioso en un pequeño porcentaje de los casos seleccionados de tuberculosis pulmonar, y defínese su limitado campo de indicaciones.

REFERENCES

Complete studies of the argument can be found in the following texts:

Ascoli, M., and Lucacer, M.: Le pneumothorax bilatèral simultanè, Masson et Cie Editeurs, Paris, 1932, p. 89.

Dumarest, F., *et al.*: La pratique du pneumothorax thèrapeutique, Ed. 4, Masson et Cie Editeurs, Paris, 1936, p. 284.

Parodi, F.: La mècanique pulmonaire, Masson et Cie Editeurs, Paris, 1933.
Repôs physiologique du poumon par hypotension, Masson et Cie Editeurs, Paris, 1935.

Salmon, J.: Essai sur la pneumothorax contralatèral, Bosc Frères, M. et L. Rion Editeurs, Lyon, 1935.

(1) Lucacer, M.: The immediate results of contralateral primary artificial pneumothorax, Am. Rev. Tuberc., 1931, *24*, 50.

(2) Ascoli, M.: Der kontralateral Tiefdruckpneumothorax, Deutsche med. Wchnschr., 1929, *33*, 1969.
Sul pneumotorace controlaterale primario, Riv. san. siciliana, 1930, *15*, 999.
Sul pneumotorace controlaterale primario, Sanatorium, 1931, p. 4.
Il pneumotorace ipotensivo: Concetto sviluppi, applicazioni—Società Lombarda di Medicina—Scritti raccolti dal Prof. F. Parodi, A. Wassermann Editore, Milano, 1936, p. 29.

(3) Bordet, F., and Parodi, F.: L'influence d'une insufflation sur le pression du cotè opposè dans le pneumothorax double, Rev. de la tuberc., 1926, *7*, 469.

(4) Lucacer, M., and Polizzotto, S.: Ripercussione dei rifornimenti pneumotoracici sulla meccanica respiratoria, Riv. di pat. e clin. d. tuberc., 1931, *11*, 968.

(5) Schill, E.: Ueber die Wirkung des einsitigen kuenstlichen Pneumothorax bei doppelseitiger Lungentuberkulose, Beitr. z. Klin. d. Tuberc., 1931, *76*, 6.

(6) Epifanio, G.: Criteri radiologici di efficienza e di tolleranza in pneumotorace artificiale, Riforma med., 1932, *5*, 155.

(7) Parodi, F.: Il concetto di ipotensione sul quale poggia l'azione controlaterale del pneumotorace—Società Lombarda di Medicina—Scritti raccolti dal Prof. F. Parodi, A. Wassermann Editore, Milano, 1936, p. 39.

(8) Gwerder-Pedojia, I.: Paradossi del pneumotorace artificiale, Tubercolosi, 1927, *4*, 137.

(9) Fiori, E.: Frenicoexeresi omolaterale e pneumotorace controlaterale primario in soggetti affetti da gravi emottisi a ripetizione—Società Lombarda di Medicina—Scritti raccolti dal Prof. F. Parodi, A. Wassermann Editore, Milano, 1936, p. 197.

(10) Pons, E.: Su di un caso di pneumotorace controlaterale per frenare emottisi ribelle del lato opposto, Tubercolosi, 1929, *11*, 467.

(11) Lucacer, M., and Lo Monaco, G.: La pressione ottimale nel pneumotorace ipotensivo, Riv. di pat. e clin. d. tuberc., 1936, *7*, 472.

(12) Ascoli, M., and Lucacer, M.: Sul pneumotorace controlaterale primario, Riforma med., 1932, *32*, 1203.

(13) Fici, V.: Osservazioni cliniche sul pneumotorace controlaterale primario—Società Lombarda di Medicina—Scritti raccolti dal Prof. F. Parodi, A. Wassermann Editore, Milano, 1936, p. 113.

(14) Malpeli, C.: Casi clinici di pneumotorace controlaterale—Società Lombarda di Medicina—Scritti raccolti dal Prof. F. Parodi, A. Wassermann Editore, Milano, 1936, p. 73.

(15) Tobè, F., Degeorges, M.e, Salmon, J., and Joly, H.: A propos du pneumothorax controlatèral, Rev. de la tuberc., 1936, *2*, 950.
A proposito del meccanismo d'azione del pneumotorace artificiale. Alcune osservazioni di pneumotorace controlaterale, Riforma med., 1935, *51*, 507.
(16) Alimenti, P.: Sul pneumotorace controlaterale primario di Maurizio Ascoli, Policlinico (sez. prat.), 1937, *44*, 2347.
(17) Bettini, D.: Sul meccanismo d'azione del pneumotorace controlaterale di M. Ascoli, Riv. Ital. della Tuberc. e della Difesa soc., 1933, *8*, 334.
(18) Botteri, G.: Di una probabile azione del pneumotorace controlaterale nei versamenti pleurici, Gior. di clin. med., 1932, *9*, 766.
(19) Carpi, U.: Un caso di tisi polmonare curato con pneumotorace controlaterale—Società Lombarda di Medicina—Scritti raccolti dal Prof. F. Parodi, A. Wassermann Editore, Milano, 1936, p. 105.
(20) Fernandez, G., and Di Salvo, A.: Sul pneumotorace controlaterale primario, Riv. san. siciliana, 1930, *15*, 1036.
(21) Fichera, S., and Giuffrida, F.: Rèsultats immediats du pneumothorax controlatèral, Rev. de la tuberc., 1930, *5*, 528.
(22) Gabriel, G.: I problemi della collassoterapia nella tubercolosi polmonare. La detensione controlaterale delle forme in sinfisi pleurica parziale o totale, Minerva med. 1936, *2*, 97.
(23) Galmozzi, F.: Un caso di pneumotorace controlaterale—Società Lombarda di Medicina—Scritti raccolti dal Prof. F. Parodi, A. Wassermann Editore, Milano, 1936, p. 191.
(24) Iacono, V.: Pneumotorace controlaterale primario di Maurizio Ascoli, Riv. di pat. e clin. d. tuberc. 1929, *3*, 989.
(25) Mendes, G.: Il pneumotorace controlaterale, Lotta contro la tuberc., 1931, *2*, 22.
(26) Dumarest, F., and Lefèvre, P.: Le pneumothorax controlatèral primitif: ses bases thèorique, Provence med., 1935, *43*, 17.
(27) Gravier-Gineste, P. E.: Contribution a l'ètude du pneumothorax controlatèral primitif, Thèse de Montpellier, 1933.
(28) Kanony, M.: Considerations sur le pneumothorax controlatèral, Rev. de la tuberc., 1936, *2*, 603.
(29) Libert, E.: Sur quelques particularitès d'un pneumothorax controlatèral, Ibid., 1936, *2*, 1200.
(30) Mantoux, E.: Pneumothorax controlatèral, Bull. et mém. Soc. méd. d. hôp. de Paris, 1930, *3*, 46.
(31) Rautoureau, F.: Un caso di pneumotorace controlaterale—Società Lombarda di Medicina—Scritti raccolti dal Prof. F. Parodi, A. Wassermann Editore, Milano, 1936, p. 195.
(32) Sivrière, F.: Contributo allo studio del pneumotorace controlaterale—Società Lombarda di Medicina—Scritti raccolti dal Prof. F. Parodi, A. Wassermann Editore, 1936, p. 221.
(33) Heudtlass, A. P., and Garrè, O.: Neumothorax controlateral, Prensa méd. argent., 1937, *24*, 1936.
(34) Renzo, A.: Neumothorax controlateral de Ascoli, Rev. Asoc. méd. argent., 1938, *52*, 383.
(35) Reginaldo, Fernandes: Pneumothorace controlateral primitivo, Rev. brasil. de tuberc., 1935, *25*, 26.
(36) Neumann, W.: L'azione di ipotensione di Ascoli dimostrata dalla guarigione delle caverne nella parte controlaterale non compressa da un pnx.—Società Lombarda di Medicina—Scritti raccolti dal Prof. F. Parodi, A. Wassermann Editore, Milano, 1936, p. 69.
(37) Beekmann, A.: Beeinflussung einer tuberkuloesen Kaverne durch kontralateralen Pneumothorax, Ztschr. f. Tuberk., 1939, *83*, 137.

QUANTITATIVE STANDARDIZATION OF TUBERCULIN PURIFIED PROTEIN DERIVATIVE[1]

LAWRENCE T. CLARK AND STEPHEN F. FOLLIN

Since the "shock" method of testing tuberculin was first instituted by Robert Koch in 1890, many tuberculins have been prepared but only a few methods have been devised for determining their activity. Tuberculins prepared according to the general principles of Koch have all been found to vary from one lot to another, due undoubtedly in part to the absence of a uniform and controlled medium on which the *Mycobacterium tuberculosis* was grown.

Ayman (1) states that with a given batch of Tuberculin Old, Koch, it is possible to determine a dilution which will give a minimum of positive reactions of a certain size in patients without active tuberculosis and a maximum of such positive reactions in patients with active tuberculosis. Assuming this possibility, it would then be necessary to determine this dilution for each batch of Tuberculin Old.

Another troublesome factor with use of Tuberculin Old is that of pseudo-reactions which may result from the use of a meat infusion or peptone base medium used in the preparation of the tuberculin.

The synthetic medium made according to the method of Dorset (2) provides a protein free medium on which the *Mycobacterium tuberculosis* develops rapidly under proper temperature conditions. It is easily prepared and by using ingredients of maximum purity provides a medium that may readily be duplicated in successive lots.

In the isolation of Tuberculin Purified Protein Derivative, Seibert (3) states that the yield varies with the strains used. Consequently those strains producing the highest yield were used.

By means of about 3,000 tests, Long, Aronson and Seibert (4) determined the potency, uniformity and reliability of Tuberculin Purified Protein Derivative in comparison with a single lot of highly potent Tuberculin Old of known value. They found that 0.000,02 mg. of Tuberculin Purified Protein Derivative gave the most satisfactory results for the initial dose, detecting a high percentage of positive reactors with a minimum of severe reactions. A second and final dose of 0.005 mg. was found to be sufficient to detect the remaining positive reactors that were negative to the first dose.

Aronson (5) states that the first strength test dose of 0.000,02 mg. Tuberculin Purified Protein Derivative is the equivalent of 0.002 mg. to 0.01 mg. of Tuberculin Old and that the second strength test dose of 0.005 mg. Tuberculin Purified Protein Derivative is the equivalent of approximately 1.0 mg.

Clinicians and research workers in tuberculosis have been hampered in obtaining accurate results because a definite reactive dose of Tuberculin Old is usually unknown unless numerous tests are conducted to determine it and then the figure is usually changed with successive lots due to a lack of uniformity.

[1] From the Research Laboratories of Parke, Davis & Company, Detroit, Michigan.

Since the potency, reliability and uniformity of Tuberculin Purified Protein Derivative has been established, we have attempted to correlate the factors relative to a definite qualitative and quantitative test upon sensitized guinea pigs. The conclusions reached in this work are based on numerous tests conducted at various times and under several conditions pertaining to the sensitization of guinea pigs and methods of procedure employed in performing the intracutaneous tests. It will be noticed, even with the methods finally adopted, that the test protocols show some variation in the size of the reactions of a single dilution from

TABLE 1

Group A

Tuberculin PPD, 1 per cent solution, B‡ 096453

Tuberculin PPD, 0.006 mg. tablet, B‡ 034139

GUINEA PIG NUMBER	DOSE (MG. IN 0.1 CC.)	24 HOUR READING (LOT 096453)	24 HOUR READING (LOT 034139)	48 HOUR READING (LOT 096453)	48 HOUR READING (LOT 034139)
	mg.	mm.	mm.	mm.	mm.
I	0.000,05	5 x 5 E	8 x 10 E	7 x 5 E	5 x 5 E
	0.000,04	7 x 10 E	10 x 15 E	7 x 7 E	3 x 5 E
	0.000,03	12 x 8 E	5 x 5 E	6 x 4 E	3 x 4 E
	0.000,02	5 x 7 E	8 x 10 E	5 x 7 E	7 x 4 E
	0.000,01	7 x 11 E	5 x 5 E	8 x 4 E	3 x 3 E
II	0.000,05	8 x 7 E	8 x 16 E	7 x 7 E	7 x 7 E
	0.000,04	12 x 8 E	8 x 16 E	7 x 7 E	8 x 8 E
	0.000,03	7 x 10 E	8 x 12 E	7 x 8 E	7 x 7 E
	0.000,02	5 x 5 E	8 x 6 E	4 x 4 E	4 x 4 E
	0.000,01	7 x 8 E	4 x 4 E	3 x 3 E	4 x 4 E
III	0.000,05	6 x 6 E	10 x 10 E	5 x 6 E	6 x 7 E
	0.000,04	5 x 5 E	5 x 5 E	4 x 4 E	7 x 7 E
	0.000,03	2 x 2 E	10 x 12 E	No reaction	6 x 6 E
	0.000,02	3 x 3 E	6 x 6 E	No reaction	5 x 5 E
	0.000,01	4 x 4 E	4 x 4 E	No reaction	2 x 3 E

E = erythema. N = necrosis.

one animal to another. The factor of individual animal variation which is always present accounts for this seeming irregularity, as the gradation of reactions is definitely in proportion to the dosage given and the variation in size of the reaction of the same dilution on several guinea pigs indicates the sensitivity of the individual guinea pig. This variation was reduced to a marked degree in the final method adopted which embodies a controlled sensitization of the guinea pig.

PROCEDURE

The solution used for dissolving the tablets of Tuberculin Purified Protein Derivative in all the tests was the same as that used by Reichel and Clark (6) for diluting the compressed tablets.

Except where otherwise indicated, the guinea pigs were all sensitized by intraperitoneal

inoculation. In all cases, human strains of *M. tuberculosis* were used and the suspension employed was no greater than the density of McFarland's nephelometer tube #1.

Group A: White or light skin guinea pigs weighing 350 to 375 g. Animal I sensitized with 0.15 cc. suspension of *M. tuberculosis* 01153 of low virulence. Animal II sensitized with 0.10 cc. suspension *M. tuberculosis* strains 01461 and 01497 combined. Animal III sensitized with 0.10 cc. suspension *M. tuberculosis* 01497 which is a virulent strain.

TABLE 2

Group B

Tuberculin PPD, 1 per cent solution, R 096453

Tuberculin PPD, 0.006 mg. tablet, R 034139

GUINEA PIG NUMBER	DOSE (MG. IN 0.1 CC.)	24 HOUR READING (LOT 096453)	24 HOUR READING (LOT 034139)	48 HOUR READING (LOT 096453)	48 HOUR READING (LOT 034139)
	mg.	mm.	mm.	mm.	mm.
I	0.000,05	6 x 7 E	8 x 8 E	No reaction	No reaction
	0.000,04	6 x 7 E	6 x 8 E	4 x 6 E	No reaction
	0.000,03	3 x 3 E	3 x 3 E	No reaction	No reaction
	0.000,02	3 x 3 E	3 x 3 E	No reaction	No reaction
	0.000,01	4 x 4 E	6 x 8 E	No reaction	No reaction
II	0.000,05	8 x 8 E	8 x 10 E	No reaction	No reaction
	0.000,04	6 x 6 E	7 x 7 E	No reaction	No reaction
	0.000,03	4 x 4 E	7 x 7 E	No reaction	No reaction
	0.000,02	4 x 4 E	7 x 7 E	No reaction	No reaction
	0.000,01	4 x 4 E	5 x 5 E	No reaction	No reaction
III	0.001	7 x 10 E	5 x 9 E	No reaction	3 x 5 E
	0.000,8	8 x 13 E	11 x 12 E	No reaction	4 x 4 E
	0.000,6	7 x 8 E	9 x 8 E	No reaction	3 x 3 E
	0.000,4	6 x 8 E	10 x 11 E	No reaction	No reaction
	0.000,1	9 x 7 E	4 x 5 E	No reaction	No reaction
	0.000,08	6 x 7 E	No reaction	No reaction	No reaction
	0.000,05	6 x 8 E	6 x 6 E	No reaction	No reaction
	0.000,03	3 x 3 E	3 x 3 E	No reaction	No reaction
	0.000,01	4 x 5 E	6 x 8 E	No reaction	No reaction
	0.000,008	5 x 5 E	4 x 5 E	No reaction	No reaction

E = erythema. N = necrosis.

One month after inoculation the hair was shaved from the ventral region for the intracutaneous test. Reactions are very irregular. Physical condition of guinea pigs—very poor.

Group B: Guinea pigs weighing 350 to 375 g. Animals I and III sensitized with 0.10 cc. suspension *M. tuberculosis* 01497 and animal II sensitized with 0.10 cc. suspension of *M. tuberculosis* 01153. Animals I and II were used for the test three weeks after inoculation and animal III, four weeks after.

For the intracutaneous test, the hair was removed from the dorsal region by shaving. Reactions very irregular. Physical condition of guinea pigs—very poor.

Group C: White or light skin guinea pigs weighing 350 to 375 g. Sensitized with 0.10 cc. suspension *M. tuberculosis*, using strain 01153 for animal I and strain 01497 for animal II.

One month after inoculation the hair was depilated from the dorsal region for the intracutaneous test. Reactions are more in keeping with gradation of doses. Physical condition of guinea pigs—poor.

TABLE 3

Group C

Tuberculin PPD, 1 per cent solution, Ⱥ 096453

Tuberculin PPD, 1 mg. tablet, Ⱥ 096198

GUINEA PIG NUMBER	DOSE (MG. IN 0.1 CC.)	24 HOUR READING (LOT 096453)	24 HOUR READING (LOT 096198)	48 HOUR READING (LOT 096453)	48 HOUR READING (LOT 096198)
	mg.	mm.	mm.	mm.	mm.
I	0.01	17 x 15 E	12 x 14 E	15 x 17 E	12 x 15 E
	0.005	11 x 13 E	14 x 16 E	10 x 12 E	11 x 12 E
	0.001	14 x 15 E	12 x 12 E	10 x 10 E	8 x 8 E
	0.000,5	14 x 15 E	9 x 10 E	10 x 11 E	5 x 5 E
	0.000,1	7 x 8 E	8 x 7 E	2 x 2 E	No reaction
	0.000,05	7 x 6 E	5 x 5 E	No reaction	No reaction
	0.000,01	No reaction	3 x 3 E	No reaction	No reaction
	0.000,005	5 x 5 E	4 x 4 E	No reaction	No reaction
	0.000,001	No reaction	No reaction	No reaction	No reaction
	0.000,000,5	No reaction	No reaction	No reaction	No reaction
II	0.005	15 x 15 E	15 x 15 E	12 x 13 E	14 x 15 E
	0.000,5	12 x 11 E	13 x 12 E	10 x 11 E	10 x 13 E
	0.000,05	8 x 8 E	10 x 11 E	5 x 5 E	No reaction
	0.000,04	7 x 8 E	10 x 9 E	5 x 5 E	6 x 7 E
	0.000,03	6 x 6 E	8 x 8 E	4 x 4 E	4 x 4 E
	0.000,02	6 x 6 E	5 x 5 E	3 x 3 E	No reaction
	0.000,01	4 x 4 E	5 x 5 E	No reaction	No reaction
	0.000,005	4 x 4 E	4 x 4 E	4 x 4 E	3 x 3 E
	0.000,001	4 x 4 E	3 x 3 E	3 x 4 E	3 x 3 E
	0.000,000,5	4 x 4 E	2 x 2 E	No reaction	3 x 3 E

E = erythema. N = necrosis.

Group D: White guinea pigs weighing 800 g. Animal I sensitized with 0.10 cc. suspension *M. tuberculosis* 01497 inoculated subcutaneously, while animal II was sensitized with same dose but with intraperitoneal inoculation.

Two months after inoculation the hair was depilated from the dorsal region for the intracutaneous test. Reactions are in proportion to dosage. Physical condition of animals—good.

Group E: White guinea pigs weighing 425 to 450 g. Both animals were sensitized by intraperitoneal inoculation of 0.10 cc. suspension *M. tuberculosis* 01497.

Two months after inoculation the hair was depilated from the dorsal region, for the

TABLE 4

Group D

Tuberculin PPD, 1 mg. tablet, R‡ 096198

Tuberculin PPD, 1 per cent solution, R‡ 096453

GUINEA PIG NUMBER	DOSE (MG. IN 0.1 CC.)	24 HOUR READING (LOT 096198)	24 HOUR READING (LOT 096453)	48 HOUR READING (LOT 096198)	48 HOUR READING (LOT 096453)
	mg.	mm.	mm.	mm.	mm.
I	0.005	22 x 20 E	20 x 20 E	18 x 22 E	17 x 18 E
		12 x 12 N	10 x 10 N	12 x 15 N	10 x 10 N
	0.000,5	17 x 17 E	13 x 13 E	16 x 17 E	15 x 13 E
		7 x 7 N		10 x 10 N	
	0.000,05	12 x 13 E	8 x 8 E	12 x 14 E	5 x 6 E
	0.000,02	9 x 9 E	5 x 5 E	9 x 9 E	No reaction
	0.000,005	7 x 7 E	3 x 3 E	7 x 7 E	5 x 4 E
	0.000,000,5	4 x 4 E	No reaction	No reaction	No reaction
	0.000,000,05	3 x 3 E	No reaction	No reaction	No reaction
	0.000,000,005	No reaction	No reaction	No reaction	No reaction
	0.000,000,000,5	No reaction	No reaction	No reaction	No reaction
	0.1 cc. diluent only	No reaction	No reaction	No reaction	No reaction

E = erythema. N = necrosis.

TABLE 5

Group D

Tuberculin PPD, 1 mg. tablet, R‡ 096198

Tuberculin Old, Koch, R‡ 036447

GUINEA PIG NUMBER	DOSE (MG. IN 0.1 CC.)	24 HOUR READING	48 HOUR READING
	mg.	mm.	mm.
II	0.005	19 x 17 E	18 x 10 E
			10 x 10 N
Left side. Tuberculin PPD, 096198	0.000,5	12 x 15 E	12 x 12 E
	0.000,05	10 x 9 E	7 x 7 E
	0.000,02	No reaction	No reaction
	0.000,005	9 x 8 E	5 x 5 E
	0.000,000,5	6 x 6 E	5 x 5 E
	0.000,000,05	5 x 4 E	No reaction
	0.000,000,005	5 x 3 E	No reaction
	0.000,000,000,5	No reaction	No reaction
	0.1 cc. diluent only	No reaction	No reaction
II	0.1 cc. of 1:100 dilution	20 x 18 E	17 x 15 E
		9 x 12 N	10 x 10 N
Right side. Tuberculin Old, 036447	1:250	16 x 12 E	13 x 15 E
		8 x 8 N	8 x 8 N
	1:500	15 x 15 E	15 x 14 E
	1:1,000	13 x 12 E	9 x 10 E
	1:5,000	9 x 9 E	9 x 9 E
	1:10,000	10 x 8 E	5 x 5 E
	1:20,000	No reaction	No reaction
	1:30,000	6 x 6 E	No reaction
	1:50,000	4 x 3 E	No reaction
	0.1 cc. diluent only	No reaction	No reaction

intracutaneous test. Reactions comparable to gradation of doses. Physical condition of guinea pigs—good.

Group F: White guinea pigs weighing 425 to 450 g. Sensitized with intraperitoneal injection of 0.10 cc. suspension *M. tuberculosis* 01497.

For the intracutaneous test, the hair was removed by depilatory from the dorsal region. Guinea pigs I and II were used one month after inoculation and III and IV

TABLE 6

Group E

Tuberculin PPD, 1 mg. tablet, Ⱥ 096198

Tuberculin Old, Koch, Ⱥ 036447

	DOSE (MG. IN 0.1 CC.)	24 HOUR READING (ANIMAL 1)	24 HOUR READING (ANIMAL 2)	48 HOUR READING (ANIMAL 1)	48 HOUR READING (ANIMAL 2)
	mg.	mm.	mm.	mm.	mm.
Tuberculin PPD, 096198. Left side	0.001	15 x 15 E	15 x 15 E	15 x 15 E	11 x 10 E
	0.000,5	14 x 12 E	15 x 12 E	14 x 13 E	10 x 9 E
	0.000,05	10 x 10 E	10 x 8 E	8 x 8 E	8 x 4 E
	0.000,02	8 x 8 E	No reaction	4 x 4 E	4 x 4 E
	0.000,005	7 x 5 E	5 x 5 E	3 x 3 E	3 x 3 E
	0.000,000,5	3 x 5 E	3 x 3 E	No reaction	No reaction
	0.000,000,05	3 x 3 E	No reaction	No reaction	No reaction
	0.000,000,005	No reaction	No reaction	No reaction	No reaction
	0.000,000,000,5	No reaction	No reaction	No reaction	No reaction
	0.1 cc. diluent only	No reaction	No reaction	No reaction	No reaction
Tuberculin Old, Koch, 036447. Right side	0.1 cc. of 1:100 dilution	20 x 18 E	20 x 20 E	18 x 15 E	17 x 17 E
	1:250	18 x 15 E	16 x 16 E	17 x 13 E	15 x 12 E
	1:500	18 x 14 E	15 x 15 E	10 x 15 E	14 x 12 E
	1:1,000	15 x 15 E	15 x 15 E	14 x 12 E	13 x 13 E
	1:5,000	8 x 8 E	10 x 12 E	5 x 4 E	5 x 5 E
	1:10,000	8 x 6 E	No reaction	No reaction	No reaction
	1:20,000	4 x 4 E	4 x 6 E	No reaction	No reaction
	1:30,000	5 x 5 E	4 x 5 E	No reaction	No reaction
	1:50,000	4 x 4 E	No reaction	No reaction	No reaction
	0.1 cc. diluent only	No reaction	No reaction	No reaction	No reaction

E = erythema. N = necrosis.

six weeks after inoculation. Doses were injected in reverse order from usual tests and in some cases the same dose injected at all ten locations. Reactions are in proportion to dosage regardless of location on animal. Physical condition of guinea pigs—good.

Group G: White guinea pigs weighing 450 g. Sensitized by intraperitoneal inoculation of 0.10 cc. suspension of *M. tuberculosis* 01497.

One month after inoculation the hair was depilated from the dorsal region for the intracutaneous test. Reactions are in proportion to dosage. Physical condition of animals—good.

DISCUSSION

The foregoing studies, in alphabetically arranged groups, present an accurate résumé of the preliminary work performed and also show how a method was established that satisfies the requirements for a definite qualitative and quantitative test. The protocols are representative of a larger number of tests conducted in each group, illustrating progression of the work step by step as the objectionable factors were eliminated.

TABLE 7

Group F

Tuberculin PPD, 1 mg. tablet, Ⱡ 096198

Tuberculin PPD, 1 per cent solution, Ⱡ 096453

GUINEA PIG NUMBER	DOSE (MG. IN 0.1 CC.)	24 HOUR READING (LOT 096198)	24 HOUR READING (LOT 096453)	48 HOUR READING (LOT 096198)	48 HOUR READING (LOT 096453)
	mg.	*mm.*	*mm.*	*mm.*	*mm.*
I	0.1 cc. diluent	No reaction	No reaction	No reaction	No reaction
	0.000,000,000,5	4 x 4 E	5 x 5 E	No reaction	No reaction
	0.000,000,005	4 x 4 E	6 x 7 E	No reaction	No reaction
	0.000,000,05	7 x 7 E	9 x 8 E	6 x 6 E	6 x 6 E
	0.000,000,5	7 x 8 E	8 x 8 E	7 x 7 E	7 x 8 E
	0.000,005	4 x 5 E	6 x 7 E	No reaction	6 x 8 E
	0.000,02	5 x 6 E	4 x 5 E	6 x 6 E	No reaction
	0.000,05	8 x 9 E	5 x 10 E	7 x 7 E	6 x 10 E
	0.000,5	10 x 12 E	9 x 11 E	10 x 11 E	9 x 9 E
	0.005	16 x 21 E (7 x 7 N)	18 x 20 E (8 x 8 N)	16 x 18 E (11 x 11 N)	20 x 20 E (10 x 10 N)
II	0.000,005	6 x 7 E	5 x 5 E	No reaction	No reaction
	0.000,02	7 x 8 E	5 x 5 E	No reaction	No reaction
	0.000,05	8 x 10 E	6 x 8 E	No reaction	No reaction
	0.000,5	14 x 14 E	13 x 14 E	15 x 15 E	10 x 11 E
	0.005	20 x 21 E (7 x 7 N)	19 x 20 E	19 x 20 E (7 x 8 N)	15 x 17 E
	0.1 cc. diluent	No reaction	No reaction	No reaction	No reaction
	0.000,000,000,5	4 x 4 E	3 x 3 E	No reaction	No reaction
	0.000,000,005	4 x 4 E	3 x 3 E	No reaction	No reaction
	0.000,000,05	3 x 3 E	No reaction	No reaction	No reaction
	0.000,000,5	No reaction	3 x 4 E	No reaction	No reaction

E = erythema. N = necrosis.

A human strain of *M. tuberculosis*, 01497, was chosen as the standard culture for sensitizing the guinea pigs. It may be noted that two other strains were employed during the preliminary work, but due to the lessened virulence of one and the seeming instability of the other, they were discontinued. The stock culture is maintained by subculturing at eight to ten week intervals, alternating the medium in rotation, between the standard 5 per cent glycerine agar and Petragnani's medium.

In the tests of the first three groups (A, B and C), guinea pigs weighing from

350 to 375 g. were used. In all cases the smaller animals were less resistant and were in very poor physical condition at the end of either three or four weeks when the tests were performed. Slightly better results may be noted in the group C test. The dorsal region was used as the site for this test and the hair was removed by a depilatory. It was observed here that, if the hair was depilated rapidly and the skin thoroughly rinsed with lukewarm water, less irritation occurred and more uniform results obtained than when either the dorsal or ventral regions were shaved.

Joyner and Sabin (7) performed intracutaneous tests with dye on tuberculous guinea pigs. According to their report the spread of the substance injected is

TABLE 8

Group F

Tuberculin PPD, 1 mg. tablet, R 096198

Tuberculin PPD, 1 per cent solution, R 096453

GUINEA PIG NUMBER	DOSE (MG. IN 0.1 CC.)	24 HOUR READING (LOT 096198)	24 HOUR READING (LOT 096453)	48 HOUR READING (LOT 096198)	48 HOUR READING (LOT 096453)
	mg.	*mm.*	*mm.*	*mm.*	*mm.*
III	0.000,02	7 x 7 E	5 x 5 E	4 x 5 E	3 x 3 E
	0.000,02	7 x 8 E	No reaction	5 x 5 E	3 x 3 E
	0.000,02	10 x 9 E	5 x 7 E	4 x 5 E	3 x 3 E
	0.000,02	5 x 7 E	7 x 8 E	7 x 7 E	4 x 6 E
	0.000,02	6 x 8 E	5 x 5 E	5 x 5 E	3 x 3 E
	0.000,02	4 x 7 E	5 x 6 E	5 x 5 E	3 x 4 E
	0.000,02	5 x 6 E	6 x 6 E	4 x 5 E	4 x 4 E
	0.000,02	6 x 7 E	6 x 7 E	4 x 5 E	4 x 4 E
IV	0.000,000,5	4 x 4 E	4 x 5 E	4 x 4 E	No reaction
	0.000,000,5	5 x 5 E	4 x 4 E	4 x 4 E	No reaction
	0.000,000,5	No reaction	No reaction	5 x 5 E	No reaction
	0.000,000,5	4 x 5 E	No reaction	5 x 5 E	No reaction
	0.000,000,5	4 x 5 E	4 x 5 E	5 x 5 E	No reaction
	0.000,000,5	No reaction	5 x 5 E	4 x 5 E	4 x 4 E
	0.000,000,5	4 x 5 E	4 x 4 E	No reaction	No reaction
	0.000,000,5	5 x 5 E	5 x 5 E	4 x 4 E	5 x 5 E

E = erythema. N = necrosis.

determined by the physical condition of the animal used. Normal guinea pigs and those in moribund or terminal stages of tuberculosis did not retain the substance at the point of injection but allergic guinea pigs in relatively good physical condition retained the dye at the point of injection with greatly retarded spread thereafter. This work was confirmed by Gottschall and Bunney (8) by using young guinea pigs. They also found that the spread of trypan blue is less in old than in young guinea pigs and that the spread in the older animals is not influenced by tuberculosis.

Our work confirms these reports since the actual sensitivity of the guinea pig and the retention of the substance at the point of injection are directly related to

the age or weight of the normal guinea pig inoculated for sensitization and to the extent of the infection produced when the peak of sensitization has been reached. When we inoculated guinea pigs weighing 350 to 375 g. the results were not uniform (groups A, B and C) and the animals were usually in the terminal stages of infection at the end of the sensitization period. When the older guinea pigs (425 to 450 g.) were used in subsequent tests, there were fewer deaths and the loss

TABLE 9

Group G

Tuberculin PPD, 1 per cent solution, Ⱥ 096453

Tuberculin Pur. Prot. Deriv., 0.05 mg. tablet, Ⱥ 058855

Tuberculin PPD, 0.025 mg. tablet, Ⱥ 058233

Tuberculin Pur. Prot. Deriv., 0.006 mg. tablet, Ⱥ 058970

	DOSE (MG. IN 0.1 CC.)	24 HOUR READING (ANIMAL 1)	24 HOUR READING (ANIMAL 2)	48 HOUR READING (ANIMAL 1)	48 HOUR READING (ANIMAL 2)
	mg.	*mm.*	*mm.*	*mm.*	*mm.*
1 per cent solution PPD 096453	0.005	13 x 13 E	14 x 15 E	10 x 12 E	15 x 15 E
	0.000,5	8 x 9 E	9 x 9 E	5 x 8 E	7 x 7 E
	0.000,05	4 x 5 E	5 x 5 E	4 x 5 E	No reaction
	0.000,02	4 x 4 E	4 x 4 E	No reaction	No reaction
	0.000,01	3 x 4 E	No reaction	No reaction	No reaction
PPD tablet 058885	0.005	15 x 13 E	15 x 15 E	15 x 12 E	18 x 18 E
	0.000,5	7 x 9 E	9 x 12 E	7 x 8 E	11 x 10 E
	0.000,05	4 x 6 E	6 x 7 E	No reaction	5 x 6 E
	0.000,02	4 x 4 E	5 x 5 E	No reaction	5 x 5 E
	0.000,01	4 x 4 E	4 x 4 E	No reaction	No reaction
PPD tablet 058233	0.005	13 x 13 E	14 x 14 E	12 x 13 E	16 x 15 E
	0.000,5	7 x 8 E	11 x 10 E	7 x 8 E	11 x 10 E
	0.000,05	5 x 5 E	7 x 7 E	No reaction	5 x 5 E
	0.000,02	5 x 5 E	4 x 4 E	No reaction	4 x 4 E
	0.000,01	4 x 4 E	4 x 4 E	No reaction	4 x 4 E
PPD tablet 058970	0.000,5	7 x 8 E	9 x 9 E	7 x 7 E	9 x 10 E
	0.000,05	5 x 5 E	6 x 6 E	5 x 6 E	5 x 6 E
	0.000,02	4 x 4 E	4 x 4 E	No reaction	4 x 5 E
	0.000,01	No reaction	3 x 3 E	No reaction	No reaction
	0.1 cc. diluent only	No reaction	No reaction	No reaction	No reaction

E = erythema. N = necrosis.

of weight was less through the month of sensitization, resulting in reactions ranging from true necrosis through lessening degrees of erythema until a complete fade-out was reached.

In Group D a comparison is made between the intraperitoneal and subcutaneous methods of inoculation for sensitization, using guinea pigs weighing 800 g. each. The larger animal affords wider spacing of doses for the reaction test

but our records show somewhat better sensitization reaction prevails with the 450 g. guinea pig. This may be noted by results of the group E test. The degree of sensitivity produced by either the subcutaneous or intraperitoneal routes

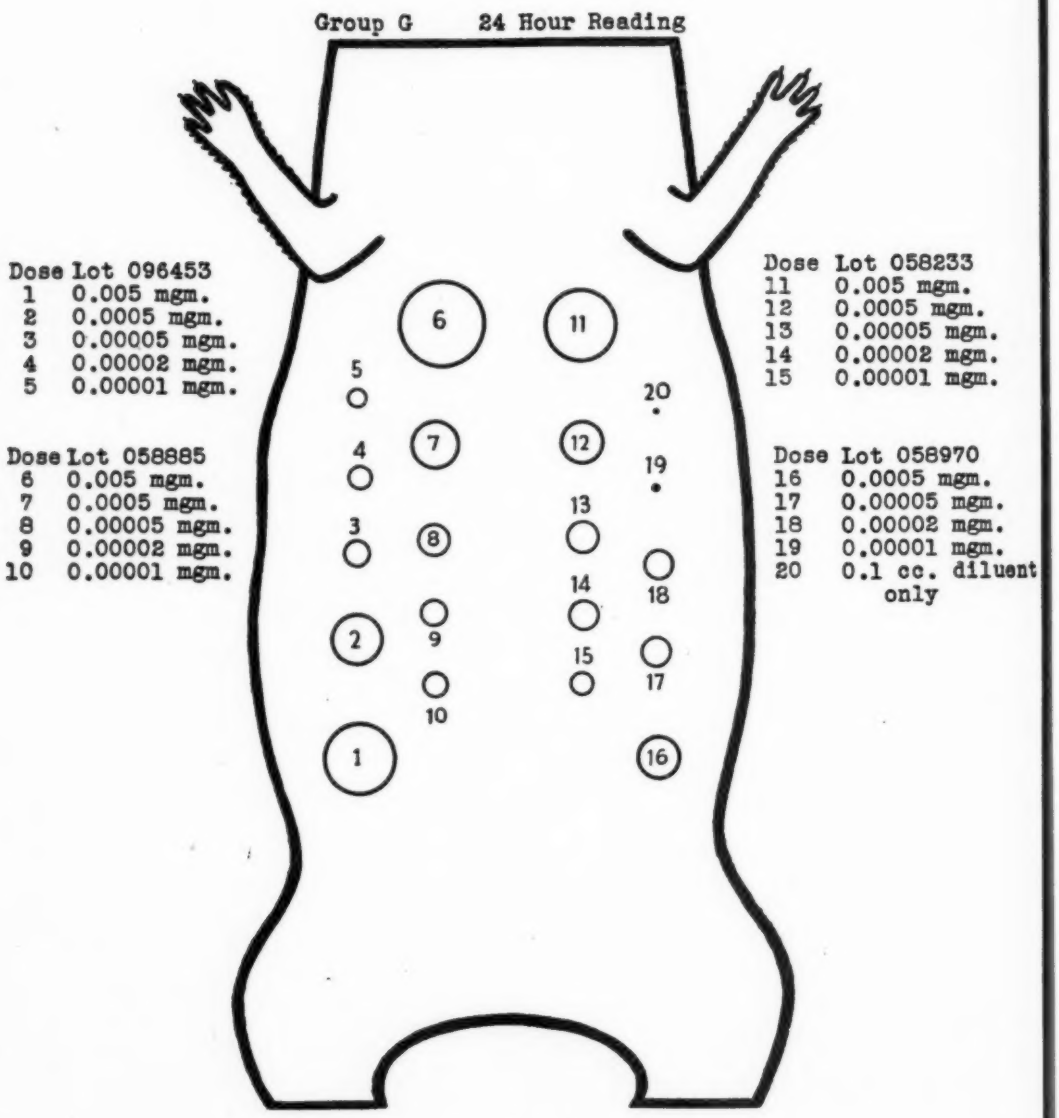


FIG. 1

compares favorably. However, from the standpoint of safety to the operators the intraperitoneal method is preferable since ulceration invariably occurs from subcutaneous inoculation of *M. tuberculosis*.

In group E we have a comparative test between the Tuberculin Purified Pro-

tein Derivative and Tuberculin Old, Koch, performed on 2 sensitized guinea pigs. The difference in size of the reactions of a single dose on the 2 animals brings to attention again the slight variation in sensitivity of the individual guinea pig. However, this variation does not alter the interpretation of the test since these are the average limits of variation encountered. Included in the series of both products are the human doses ordinarily used.

Seibert and Morley (9) working with several strains of tubercle bacilli report a wide variation in the sensitivity produced by each strain in guinea pigs. The limits of sensitivity ranged from that too low for any quantitative study to so highly reactive that 0.000,002 mg. of purified tuberculin protein or 0.10 cc. of a 1:500,000 dilution of Old Tuberculin gave a large skin reaction with necrosis. By using the method we have established, it is possible to avoid these extreme variations. The elimination of certain strains of tubercle bacilli, as previously mentioned, and continuing the use of a single virulent culture has made it possible to establish a nearly uniform degree of sensitivity in 450 g. guinea pigs.

In group F we have attempted to establish the validity of our claims for the quantitative reaction by rearrangement of the order of doses (guinea pigs I and II) and by using a single dilution injected at all locations in the depilated area (guinea pigs III and IV). On the first 2 animals it appears that regardless of the location of any single injection the reaction obtained is within the slight limits of variation previously referred to. On guinea pigs III and IV with one exception (injection #3, 096198, guinea pig III) the reactions compare as favorably. It must be considered also that with this small amount of the Tuberculin Purified Protein Derivative the non-retention of the drum-like bleb or a slight excess injected will be evident in the reading.

In group G we present a very recent test evaluating the reactivity of four lots of Tuberculin Purified Protein Derivative on each of 2 guinea pigs sensitized in the manner mentioned above. The uniformity of these reactions is clearly defined with each single dose, regardless of the lot but varying slightly on the 2 guinea pigs.

Throughout all tests a 1 cc. tuberculin syringe with 25 gauge $\frac{5}{8}$ in. long bevel needle was used.

SUMMARY

As a result of the detailed accounts given of many tests under various conditions we present the following method for the quantitative standardization of Tuberculin Purified Protein Derivative:

(*a*) Select white or very light skin guinea pigs weighing 425 to 450 g. and inoculate intraperitoneally with 0.10 cc. of a suspension of virulent human type *M. tuberculosis* (01497). Density of suspension to be equal to or no greater than #1 tube McFarland's nephelometer (10). Record weight of guinea pigs when inoculated and weekly after second week.

(*b*) After a four week sensitization period, choose those guinea pigs that have lost some or have maintained their original weight and discard those with extreme loss of weight. Use 2 sensitized guinea pigs and one normal guinea pig (375 to 450 g.) for control for each test, each animal to be used but once. Clip

and depilate the entire surface of the back and sides, rinsing thoroughly. While skin is still soft and pliable inject intracutaneously 0.10 cc. doses from each of the following freshly prepared dilutions of the product under test. Make all dilutions with Buffered Diluent for Tablets Tuberculin Purified Protein Derivative (6).

Dilutions

0.10 cc. of a dilution containing 0.05 mg. per cc. = 0.005 mg. dose
0.10 cc. of a dilution containing 0.005 mg. per cc. = 0.000,5 mg. dose
0.10 cc. of a dilution containing 0.000,5 mg. per cc. = 0.000,05 mg. dose
0.10 cc. of a dilution containing 0.000,2 mg. per cc. = 0.000,02 mg. dose
0.10 cc. of a dilution containing 0.000,1 mg. per cc. = 0.000,01 mg. dose

(*c*) *Control:* On the opposite side of the median line inject intracutaneously 0.10 cc. doses of like dilutions of the standard for comparison.

(*d*) Record reactions at twenty-four and forty-eight hour intervals, noting entire area of eyrthema and concentric area of blanching, oedema or necrosis. Upon close observation the true erythema may be observed at the site of the high dilutions on the sensitized guinea pig contrasted to the slight trauma from the injection in the normal guinea pig.

CONCLUSION

A method is presented whereby a quantitative standardization of Tuberculin Purified Protein Derivative may be accomplished; it is dependent on the use of controlled sensitization of the guinea pig. When utilizing this method of procedure a given dose of Tuberculin Purified Protein Derivative will produce a reaction of a given size and intensity, the results being comparable within reasonable limits of variation from one guinea pig to another.

CONCLUSIONES

Preséntase un método que permite normalizar cuantitativamente el P.P.D., o sea el Derivado Proteínico Purificado de Tuberculina; la técnica se funda en el empleo de una sensibilización comprobada en el cobayo. Cuando se utiliza este procedimiento, una dosis dada de P.P.D. producirá una reacción de tamaño e intensidad dada, siendo el resultado comparable, dentro de límites razonables de variación, de un cobayo a otro.

REFERENCES

(1) Ayman, David: J. A. M. A., 1934, *103*, 154.
(2) Dorset, M.: J. Am. Vet. M. A., 1934, *84*, N.S. *37*, 439.
(3) Seibert, Florence B.: Supplement to Am. Rev. Tuberc., 1934, *30*, 713.
(4) Long, E. R., Aronson, J. D., and Seibert, F. B.: Supplement to Am. Rev. Tuberc., 1934, *30*, 733.
(5) Aronson, J. D.: Supplement to Am. Rev. Tuberc., 1934, *30*, 727.
(6) Reichel, John, and Clark, L. T.: Supplement to Am. Rev. Tuberc., 1934, *30*, 721.
(7) Joyner, A. L., and Sabin, F. R.: J. Exper. Med., 1938, *68*, 325.
(8) Gottschall, R. Y., and Bunney, W. E.: J. Immunol., 1940, *38*, 345.
(9) Seibert, F. B., and Morley, N.: Ibid., 1933, *24*, 149.
(10) Kolmer and Boerner: Approved Laboratory Technique, 1931, p. 400.

TUBERCULIN REACTION IN TUBERCULOSIS DURING PREGNANCY[1]

M. R. LICHTENSTEIN

Some authors have stated that the occurrence of pregnancy in a tuberculous patient is commonly credited with causing anergy to tuberculin. Search of the actual work done on the problem reveals that it is open to much criticism; unstandardized tuberculins were used; the Pirquet test, a relatively unreliable method for adults, was frequently used; when the intracutaneous test was used only a single dose was usually given; protocols of actual testing and controls are almost nonexistent; the term anergy is loosely applied.

Nobecourt and Paraf (1) state that 15 to 20 per cent of pregnant patients lose their skin reactivity in the last trimester. Salmond (2) believes the skin reaction is depressed in the latter months and increases after labor. Gross (3) speaks of the "anergy of gravids" in the first trimester. Coulaud (4) states that pregnancy, puberty, menstruation and abortion all cause marked depressions of allergy.

OBSERVATIONS DURING PREGNANCY

During the period from 1932 to 1941 tuberculin testing of about 8,000 patients at the Municipal Tuberculosis Sanitarium of Chicago included 82 pregnant patients with 84 pregnancies and afforded an opportunity for careful study and comparison.

Old Tuberculin (Parke, Davis & Company) was used in dilutions. It was standardized by comparison with PPD on opposite arms of a series of patients, once a year, and it was found that 1:100 OT was equal to the second strength of PPD. Dilutions 1:10,000, 1:1,000, 1:100 and 1:10 were prepared every week and kept on ice. The weakest dilution, 1:10,000, was first injected intracutaneously in a standard volume of 0.05 cc. and read at forty-eight hours. If negative, each of the succeeding strengths was used at forty-eight-hour intervals until a positive reaction occurred or all were tried. Transverse diameters of any induration palpable to the finger were recorded. Patients were considered completely insensitive if they failed to react to the 1:10 dilution, according to D'Arcy Hart. Retests were made every two months, whenever possible, on the pregnant patients for the purpose of studying any possible fluctuations in allergy. A small group of the patients were tested with 1:100,000 and 1:10,000 dilutions simultaneously at weekly or monthly intervals.

The patients studied included 57 who delivered (47 normal labors, 6 Caesarian sections, 3 premature births, one still-birth), 11 pregnancies terminated by curettement and 16 patients either are still pregnant, disappeared or expired without delivering. Nine patients were classified as minimal on entrance to the Sanitarium, 13 as moderately advanced and 60 as far advanced.

Follow-up of the patients studied revealed: 29 dead; 22 delivered (14 normal,

[1] From the Municipal Tuberculosis Sanitarium, Chicago, Illinois.

3 premature, 1 still-birth and 4 Caesarian sections); 5 curettements; 2 terminations unknown.

Table 1 shows the number of patients opposite the weakest concentration to which they reacted at different periods during and after pregnancy. Data on the first and second trimester are meagre because many patients come to the institution late in pregnancy.

In analyzing the data, two methods were used: first the curve of reactivity of each patient was studied; and, second, the reactivity of the patient was compared with that of patients with the same extent of disease, severity of symptoms and duration of disease, as established in tables presented in a previous communication (5).

TABLE 1

Tuberculin sensitivity during and after pregnancy

TRIMESTER	1ST	2ND	3RD	POSTPARTUM
Number of patients.....	9	41	56	58
Positive to:				
1:10,000.....	6	36	37	52
1:1,000.....	1	5	16	5
1:100.....	2	0	3	1

TABLE 2

Percentages of tuberculous patients reacting to OT 1:10,000

Patients:	
56 in (3rd trimester).....	66
34 (postpartum).....	82
384 nonpregnant females with far advanced tuberculosis.....	76
46 nonpregnant females with far advanced tuberculosis, C.....	61

In the first two trimesters the reactivity of the pregnant compares closely with the nonpregnant patients. The numbers are too few, however, for accurate analysis.

In the last trimester a definite depression of allergy is seen among some of the pregnant patients, that is, a larger percentage fail to react to the 1:10,000 dilution and fall in the 1:100 and 1:1,000 group than among similar nonpregnant patients (table 2).

Three patients who reacted at the 1:100 level were all very ill and died shortly. The reactivity of these 3 corresponds closely with that of many nonpregnant moribund patients.

In the group of 13 which failed to react to 1:10,000 OT but did react to 1:1,000, 5 ultimately died. The depression of sensitivity in this group cannot, however, be attributed to the degree of illness of the patients. Most of them were fever-free, not toxaemic and not acutely ill at the time tests were done. Ordinarily we

find that 75 per cent of patients in approximately the same condition react at the 1:10,000 level.

Of 37 patients who reacted at the 1:10,000 level, 2 died within a few months. Analysis of the case records discloses no special reason why this group gave the usual degree of reactivity to tuberculin, whereas the 13 mentioned above showed a depression of sensitivity.

Tests postpartum were made on 58 patients; 52 reacted to 1:10,000 and 5 to 1:1,000; one of the latter was extremely ill; 8 of the 16 patients who reacted only to 1:1,000 or 1:100 before delivery, reacted to 1:10,000 OT after delivery (within two months).

The above analysis considers only fluctuations which involved a change in the dilution required to obtain a reaction. There were, of course, many minor variations in the size of the reactions obtained to the same dilutions at various times.

DISCUSSION

The data at hand indicate that the term "anergy of gravids" is far from correct. In no instance was a pregnant tuberculous patient completely insensitive to tuberculin. The most that can be said is that a mild depression of sensitivity occurs in the third trimester in a considerable fraction of pregnant tuberculous patients. This group usually reacts at the 1:1,000 level instead of the expected 1:10,000 level. Many show only a decrease in the size of the reaction to the same dilution. Such a change can hardly be classified as anergy.

A possible explanation for the depression of allergy may lie in the presence of so much additional tissue (foetus, uterus and placenta) to take up the sensitizing agent, thus causing a general lowering of reactivity. This fails to account for the fact that some of the patients maintain the high level of reactivity throughout pregnancy. It is also difficult to understand why the sensitizing agent, which apparently must be carried by the blood and tissue fluids to sensitize all the tissues of the body, does not sensitize the foetus. It may be that the sensitizing antibody cannot pass the placental filter or that the tissues of the foetus are incapable of being sensitized because of their early stage in the evolutionary process. Tuberculin-type hypersensitivity is a relatively late occurrence in the evolution of immunological mechanisms.

CONCLUSIONS

Tuberculin sensitivity in pregnant patients with tuberculosis was studied in 82 patients. In most instances the level of reactivity is closely comparable to similar but nonpregnant patients. In about one-fourth of the pregnant patients a marked depression of sensitivity occurs in the third trimester. Shortly after delivery most of these tend to return to the normal level.

CONCLUSIONES

En 82 tuberculosas embarazadas se estudió la sensibilidad a la tuberculina, y en la mayor parte el coeficiente de reactividad resultó bastante comparable a

lo observado en las enfermas semejantes no embarazadas. Aproximadamente en la cuarta parte de las embarazadas obsérvase en el tercer trimestre una decidida baja de la sensibilidad, pero poco después del parto la mayoría recobran las cifras normales.

REFERENCES

(1) Rist, E.: Brit. M. J., 1927, *2*, 247; Rev. de la tuberc., 1921, *2*, 244.
(2) Salmond, M.: Brit. J. Tuberc., 1931, *25*, 179.
(3) Gross, E.: Zentralbl. f. Gynäk., 1927, *51*, 744.
(4) Coulaud, H.: The skin reaction in tuberculous women during the menses and after oophorectomy, Soc. med. des hôp., February 11, 1921, p. 155.
(5) Lichtenstein, M. R.: Am. Rev. Tuberc., 1934, *30*, p. 214.

THE EFFECT OF PREGNANCY UPON EXPERIMENTAL TUBERCULOSIS IN RABBITS[1]

LEO J. WADE[2]

Few clinical problems have incited more discussion than that presented by pregnancy in the tuberculous patient. No attempt will be made to review the very extensive literature of the subject, for many such reviews are extant. Most of these have to do with the comparison of statistics accumulated in various clinics. In his brief but excellent review of the subject, Fishberg points out that there is such great variability in the statistics presented that one must conclude that most of them are either inaccurate or based upon clinical observations that are not comparable (4). Other writers have pointed out the numerous difficulties involved in arriving at any definite conclusion from such data (5, 7).

Observations on experimental animals have been few. In 1907, Hermann and Hartl reported that 71.2 per cent of guinea pigs with pulmonary tuberculosis were adversely affected by pregnancy (6). The same experiments were repeated by Müller, who concluded that pregnancy has a favorable influence upon the course of the disease, but the evidence upon which his opinion is based is not recorded (8). In 1916, Norris stated that pregnancy definitely shortens the life span of tuberculous guinea pigs (10). Bogen was unable to find that pregnancy has any influence upon the course of tuberculosis in guinea pigs (2, 13). He did note, however, that animals infected early in pregnancy showed slightly less tuberculosis than the controls. The reverse was apparently true for animals infected late in pregnancy, but the differences were very slight and of questionable significance. In 1936 Schmidt-Lange reported that there was no evidence that pregnancy has a deleterious effect upon the course of tuberculous infections in white mice or guinea pigs (12). Recently Burke has found that pregnancy has no apparent effect upon the course of pulmonary tuberculosis in rabbits (3).

The object of the present experiments was to determine whether or not "pregnancy" in the broadest sense of the word, that is, including parturition, lactation and the puerperium, has any influence upon the course of experimental pulmonary tuberculosis.

The choice of an animal for experiments on tuberculosis or pregnancy has obvious difficulties. Neither human nor bovine tubercle bacilli are adjusted in virulence to any of the ordinarily available laboratory animals so as to reproduce the accurate adjustment which usually exists between the invasiveness of the human tubercle bacillus and the resistance of the human host. The choice of an animal for observation concerning pregnancy is equally difficult. The very practical considerations concerning ease of breeding, duration of gestation, etc., are insignificant in comparison to many known, and possibly even more numerous unknown differences in physiology and chemistry. Considerable experience

[1] From the Department of Pathology, Cornell University Medical College, and the New York Hospital, New York, New York.

[2] 1515 Lafayette Avenue, St. Louis, Missouri.

in this laboratory (11) has demonstrated that the intravenous inoculation of tubercle bacilli of the Ravenel strain in the rabbit produces a chronic infection, predominantly pulmonary, which resembles human tuberculosis in many respects. It differs from the chronic disease seen in man in at least one important respect, namely, that it is invariably fatal.

METHODS

Approximately 50 New Zealand white rabbits, weighing about 2,000 g. each, were placed in individual cages in the same room. Following observation for a few days they were tested with Old Tuberculin and in all instances found to be tuberculin-negative. Each animal was then inoculated with 0.000,01 mg. of tubercle bacilli, the organisms being introduced into the marginal vein of the ear. The Ravenel strain of bovine tubercle bacilli was grown on glycerin agar slants for four to six weeks. Bacteria removed from the agar slants were weighed, ground in a mortar and then suspended in physiological salt solution so that 1 cc. contained the infecting dose.

The individual animals were then designated as "control" or "experimental" by marking cages at random. The experimental animals were impregnated at variable periods of time after onset of the infection, several noninfected male rabbits being kept for this purpose. The date of copulation was recorded and the abdomens of the animals palpated twelve to fourteen days later to determine if pregnancy had occurred. If the animals were not pregnant, copulation was repeated. Several days prior to delivery the animals were removed to breeding cages and furnished with material for the construction of a nest. The animals were encouraged to nurse their young but refused to do so in some instances. The young were separated from the mother after four weeks.

Tuberculin and complement fixation tests were done at intervals of two to four weeks. Old Tuberculin was injected intracutaneously (0.2 cc. of a 1 in 5 dilution or 40 mg.) and the diameter of the area of inflammatory oedema was measured forty-eight hours later. Blood for complement fixation tests was obtained from the marginal veins of the ear just before tuberculin testing. The serum was removed by centrifugation and then heated for thirty minutes at 55°C. The suspension of the Ravenel strain of tubercle bacilli, used as antigen, was prepared by suspending a culture of the organisms with the aid of grinding in saline solution so that 1 cc. of the suspension contained 10 mg. of tubercle bacilli. The suspension was then heated for thirty minutes at 60°C. and 0.35 per cent tricresol was added as a preservative. The serum to be tested was mixed with the antigen suspension and complement (guinea pig serum) and incubated in a water bath for one hour at 37°C. Rabbit serum containing 2 units of a haemolysin and a 5 per cent suspension of sheep cells were then added to the mixture and these again were incubated in the water bath until the reaction caused by the control serum indicated the completion of the reaction. To check the accuracy of the tests, a standard serum obtained from a rabbit immunized by a series of injections of heat-killed tubercle bacilli was included in each test.

RESULTS

In figures 1 and 2 the fates of the two groups of animals are compared graphically. Two criteria have been used for this comparison, namely, the duration of life and the extent of the disease of the lungs. Of these, the duration of life is the more significant, for, with few exceptions, death does not occur until the disease is far advanced. In these experiments, as in others reported from this laboratory (12), intravenous inoculation of tubercle bacilli produces in the

rabbit an infection which is predominantly pulmonary. The proportion of the cut-surface of the lung occupied by tuberculous lesions serves as a fairly ac-

FIG. 1. In this figure each of the control rabbits is represented by a horizontal line. The length of the line indicates the duration of life after infection. The width of the line indicates the relative extent of tuberculosis of the lung, the broadest line representing involvement of 90 per cent or more of the cut surface and the narrowest lines 20 per cent or less.

curate index of the extent of the disease. Slight or moderate renal and intestinal lesions are common in animals with advanced pulmonary lesions.

Several animals were lost due to unavoidable accidents having nothing to do

with either the infection or the pregnancies. Twenty animals remain in the control group and 23 in the experimental group. The average duration of life after infection is longer in the group of tuberculous animals that became

FIG. 2. Same as figure 1, except that each line represents a member of the experimental group. Above each of these lines is one or more rectangles to indicate the time and duration of pregnancy (open rectangle) and lactation (shaded rectangle).

pregnant one or more times (224.7 days) than in the control group of tuberculous female rabbits that did not become pregnant (184.8 days). Four of the experimental animals were especially long-lived and it was necessary to sacrifice the

last surviving animal after 470 days in order to terminate the experiment. It would appear, therefore, on examination of figures 1 and 2, that pregnancy had a beneficial effect upon the life expectancy of the tuberculous animals. If these data are subjected to statistical analysis, however, the mean duration of life for the control group is 185 days and that for the experimental group is 224.5 days. Since the difference between these two means (39.5 days) is less than four times the probable error of the difference (18.4 days), the longer average survival time of the experimental animals is probably not significant.

Death followed shortly after delivery in at least 6 instances. This was of special interest to us, inasmuch as clinicians have noted that patients with tuberculosis may do poorly after delivery. Comparison of figures 1 and 2 shows that this relation is probably not significant. In none of the animals with death following shortly after gestation was the spread of the disease extensive. The detrimental effect of the pregnancy upon the tuberculosis is therefore not evident.

Pulmonary lesions were less extensive in animals permitted to become pregnant than in the control group, the average involvement of the former being 52 per cent of the cut-surface of the lung as compared to 58 per cent for the control group. Statistical study of these data reveals a mean of 52.0 per cent for the control group and 60.0 per cent for the experimental group. The probable error of difference between the two means is 7.05 per cent, indicating that the observed difference of 8.0 per cent is statistically insignificant.

It will be noted that multiple pregnancies (2 or 3) have occurred in most of the long-lived animals but 2 pregnancies have not prevented early death in several animals.

Lactation pursued its course in approximately a third of the pregnant animals but no conclusion concerning its effect upon tuberculous infection is possible. It is noteworthy that most of the long-lived animals did nurse their young without untoward results.

The results of tuberculin tests are presented in table 1. Most pregnancies have occurred between the tenth and eighteenth weeks after infection. Comparison of the tuberculin responses during this period shows no difference between the two groups. It is noteworthy that a negative response has been frequent in the period following the termination of the pregnancies, indicated by the low average response of 0.1 in the twenty-second week for the pregnant animals as compared with 1.8 in the controls. In numerous instances in which several pregnancies have occurred, the tuberculin test has become negative or very weakly positive after the termination of each of the pregnancies and has then returned to its previous value. In the few instances in which the tuberculin test has decreased or become negative during pregnancy the tuberculin test has not returned to its previous value but has declined further or remained negative and early death of the animal has ensued. As loss of sensitization usually occurs before death, it is not in these instances necessarily an effect of pregnancy.

Complement fixation tests reveal a slight lag in the appearance of complement fixing antibodies during the period of gestation (table 2). Following the termi-

nation of the pregnancies, however, little or no difference between the response of the control and experimental animals is apparent.

TABLE 1

Progress of sensitization as measured by the tuberculin test. The number of animals showing the response indicated in the column on the left is stated for various intervals after inoculation

DIAMETER OF INFLAMMATORY REACTION		PREGNANT									CONTROL								
		After 2 weeks	After 6 weeks	After 10 weeks	After 14 weeks	After 18 weeks	After 22 weeks	After 26 weeks	After 30 weeks	After 34 weeks	After 2 weeks	After 6 weeks	After 10 weeks	After 14 weeks	After 18 weeks	After 22 weeks	After 26 weeks	After 30 weeks	After 34 weeks
mm.																			
0	0	23	4	7	6	12	14	11	5	4	19	6	7	8	10	2	4	1	3
1–9	+		4	3	5	3	1	1				1		3	2	1		1	
10–19	2+		8	2	4	3		1	1			4	3	3	1	4	1	1	1
20–29	3+		4	7	4	3		1	1	2		5	6	2	2	3	1	2	
30–39	4+		1	3	2	1			2		1	4	2	3	2		1	1	
40–49	5+			1															
50–59	6+		2																
60–69	7+												2						

TABLE 2

Progress of antibody formation as measured by the complement fixation test. The number of animals showing the response indicated in the column on the left is stated for various intervals after inoculation

TITRE		PREGNANT									CONTROL								
		After 2 weeks	After 6 weeks	After 10 weeks	After 14 weeks	After 18 weeks	After 22 weeks	After 26 weeks	After 30 weeks	After 34 weeks	After 2 weeks	After 6 weeks	After 10 weeks	After 14 weeks	After 18 weeks	After 22 weeks	After 26 weeks	After 30 weeks	After 34 weeks
0	0	23	23	21	20	14	13	5	5	5	20	20	14	12	8	7	5	2	4
5	+			2	2	3	2	4	2	1			5	3	5		1	4	
10	2+					5		2	2	1			1	2	2	1	2	1	
20	3+							1		1				1	2	1			
40	4+							1	1									1	
80	5+							1						1				1	

No known abortions have occurred, delivery taking place regularly on the twenty-eighth to thirtieth day of gestation. The litters have consisted of 8 to 10 young in most instances and on gross inspection and young have appeared in all instances to be well developed and free of infection. Tuberculin tests have been done on those surviving four weeks or more and have been negative.

DISCUSSION

Previous observations concerning the immunological response in tuberculosis during pregnancy have been confined to human patients. Bar has found the tuberculin test negative in many instances and weakly positive in others (1). He has ascribed this change to an anergic state produced by the pregnancy. Others have claimed that the tuberculin test is frequently negative or weakly positive. Nobecourt and Paraf state that the tuberculin test is negative in 15 or 20 per cent of women with pregnancy (9). Stern has reported similar findings and has expressed the opinion that the immune bodies are bound to the blood lipoids which are increased during pregnancy (14).

No attempt will be made to analyze further the factors which might affect either the pregnancy or the tuberculosis. It is important to point out, however, that many factors, such as variations in age, the individual's nutritional state, the virulence of the invading organisms, the economic status of the patient, sociological problems, and numerous other factors, all of which are difficult to evaluate in any statistical study of clinical material, have been reduced to common factors in our control and experimental groups of animals.

SUMMARY

The average duration of life following tuberculous infection in rabbits undergoing from one to three pregnancies was longer than that of tuberculous rabbits which did not become pregnant, but statistical analysis indicates that the difference is too small to be significant.

The average extent of the disease at death was less in the pregnant animals than in the control animals. Again, statistical analysis reveals that the difference is too small to be significant.

Pregnancy in tuberculous animals was not accompanied by any change in sensitization to tuberculin, but following the termination of pregnancy there was a transient decrease in the intensity of the skin reaction to tuberculin.

The appearance of complement fixing antibodies for the tubercle bacillus was retarded in those infected animals that became pregnant, but following the termination of pregnancy the titres rose to the level of those in the control group.

SUMARIO

La duración media de la vida, después de una infección tuberculosa, en conejas que experimentaron de uno a tres embarazos fué mayor que en las conejas tuberculosas que no quedaron preñadas, pero el análisis estadístico indica que la diferencia no reviste importancia.

La extensión media de la enfermedad a la muerte fué menor en los animales embarazados que en los testigos, pero el análisis estadístico revela de nuevo que la diferencia es demasiado pequeña para que revista importancia.

En los animales tuberculosos la preñez no se acompañó de ningún cambio en la sensibilización a la tuberculina, pero después de terminar el embarazo se

observó una disminución transitoria en la intensidad de la cutirreacción a la tuberculina.

En los animales que quedaron embarazados se demoró la aparición de anticuerpos fijadores del complemento para el bacilo tuberculoso, pero después de terminar la preñez los títulos se elevaron al mismo nivel que en el grupo testigo.

The author wishes to express his sincere thanks to Dr. Eugene L. Opie for his valuable suggestions and interest in this investigation.

BIBLIOGRAPHY

(1) Bar, P.: Der Einfluss der Schwangerschaft auf die Tuberkulose, Rev. esp. de obstetr. y. ginecol., 1921, Nr. 65. Reviewed in Zentralbl. f. Gynäk., 1923, *47*, 290.

(2) Bogen, Emil: Experimental tuberculosis in guinea pigs, Tr. Nat. Tuberc. A., 1932, *28*, 163.

(3) Burk, Hugh E.: Pregnancy and experimental pulmonary tuberculosis in rabbits, Surg., Gynec. & Obst., 1940, *71*, 615.

(4) Fishberg, Maurice: Pulmonary Tuberculosis, vol. II, Lea & Febiger, Philadelphia, 1932, p. 179.

(5) Forssner, H.: Les rélations entre l'état de gestation et la tuberculose, Rev. de la Tuberc., 1924, *5*, 730.

(6) Hermann, Edmund, and Hartl, Rudolf: Der Einfluss der Schwangerschaft auf die Tuberkulose der Respirationsorgane, Ztschr. f. Hyg. u. Infektionskr., 1907, *56*, 231.

(7) Krause, Allen K.: Editorial, Am. Rev. Tuberc., 1935, *31*, 254.

(8) Müller, V.: Tuberculosis of lungs and pregnancy, Casopis Lekaruv Ceskych, Prague, 1923, *62*, 34.

(9) Nobecourt, P., and Paraf, J.: Loss of allergy in pregnancy, Cited by Rist, E.: in Brit. M. J., 1927, *11*, 247.

(10) Norris, C. C.: Tuberculosis and pregnancy, Am. J. Obst., 1916, *73*, 997.

(11) Opie, E. L., and Freund, Jules: An experimental study of protective inoculation with heat-killed tubercle bacilli, J. Exper. Med., 1937, *66*, 761.

(12) Schmidt-Lange, W.: Experimentelle Untersuchungen über den Einfluss der Schwangerschaft auf den Verlauf der tuberkulösen Infektion, Arch. f. Hyg., 1936, *115*, 221

(13) Skillen, J., and Bogen, E.: Pregnancy and tuberculosis, J. A. M. A., 1938, *111*, 1153.

(14) Stern, R.: Systematische Untersuchung über die lokalen Tuberkulinreaktionen in der Schwangerschaft und in Wochenbett, Ztschr. f. Geburtsh. u. Gynäk., 1910, *66*, 532.

A METHOD FOR STUDIES IN CHEMOTHERAPY OF TUBERCULOSIS[1]

The Use of a Piscine Infection

W. HARRY FEINSTONE

The introduction of sulfonamide compounds as agents for the treatment of a wide variety of bacterial infections led a number of investigators (1, 2, 3, 4) to study the action of these drugs upon experimental as well as clinical tuberculosis. While the results of these investigators have not yet yielded a practical chemotherapeutic agent, there are ample indications that this group of compounds possesses some activity, and that further work offers hope for finding a therapeutic agent for at least some forms of tuberculosis. Such work is being carried on in many laboratories. By necessity this work must, in part, take the form of testing compounds of a wide variety of structures, just as has been and is being done relative to other bacterial infections.

In the case of tuberculosis the use of guinea pigs or rabbits has been standard practice for many years. The difficulty in using these animals for testing potential chemotherapeutic agents is that such large amounts of experimentally produced synthetic compounds are required as to make the experiment often prohibitive in cost.

Experience with mammals has shown that the doses of sulfonamide compounds must be relatively large to produce adequate concentrations of the drug in the blood. With guinea pigs, doses of 300 to 500 mg. daily have been commonly used. Therefore, in performing an experiment on 10 guinea pigs over a minimum sixty-day period, 180 to 300 g. of material is required. It has been our experience that such large amounts of new synthetic compounds cannot be produced under ordinary circumstances. The result has been that hundreds of compounds that have appeared in the literature have never been studied for their effect on experimental tuberculosis, even though it may have been particularly desirable to do so.

Under these circumstances it was thought that an *in vivo* method for studying the effect of a chemical agent upon experimental tuberculosis, that required small amounts of the chemical substance, would be desirable. Toward this end goldfish were placed in tanks containing a 10-mg. per cent solution of sulfanilamide in water. At intervals, fish were removed and washed with water. The animal was sacrificed and internal tissues were removed without contamination from the surface or from the gastro-intestinal tract. This tissue was quantitatively analyzed for sulfanilamide by the Marshall method. The results showed that within three to four hours goldfish absorb sulfanilamide from the 10-mg. per cent solution in which they were contained to the extent of coming to equilibrium with the concentration in the water. The concentrations of the drug in the tissues of these fish ranged from 8 to 10 mg. per cent. Further experiments indicated that this

[1] From the Stamford Research Laboratories of the American Cyanamid Company, Stamford, Connecticut.

was also true of sulfapyridine, sulfathiazole and other sulfonamide compounds. The experiment was further confirmed upon a large carp weighing about five pounds. This fish was put into a tank containing 5 mg. per cent of sulfanilamide and eighteen hours later venous blood was obtained entirely free from contamination by the water. An analysis showed the blood to contain 4.5 mg. per cent of sulfanilamide.

Having determined that potentially therapeutic concentrations of drugs may be obtained in the blood and tissues of fish through absorption from their habitat, experimental infections were then produced with a strain of tubercle bacillus from fish, *Mycobacterium marinum*.[2] The infection was accomplished by the intraperitoneal injection of 0.03 cc. of a saline suspension of organisms from a two-week old culture of *M. marinum*. The suspension was made up to contain from 10 to 15 organisms per oil immersion field. Following infection the fish were divided into groups of 10 corresponding to the number of drugs being tested and adequate controls. Each group was maintained in an individual tank containing the desired concentration of drug under test. Each tank was equipped with apparatus for aeration and filtration. Filtration was accomplished through charcoal filters attached to the tanks, and aeration was effected (pressure 4 lbs. per square inch) through stone releasers. This air pressure is also sufficient to operate the filters. The entire assembly is available in any good commercial pet shop that specializes in aquaria and fish.

The infection did not cause death in fish up to three months from the time of inoculation, but it was observed that definite multiplication of the organisms was evident from two weeks on. The multiplication of organism was accelerated by maintaining the fish at a temperature of 30°C. The experiment was finally reduced to an arbitrary standard of twenty-one days. At the end of this time the animals were sacrificed and the drug concentrations in the tissues were determined. In addition, two slides were smeared from each animal. The first was made from the intestines and the other from the remaining viscera. The technique of smearing aimed at thorough mixing of the organs directly on the slide to leave a good smear. The excess material was then removed and the smears were stained by the Ziehl-Neelsen method.

Upon examination of these smears from the control group of fish and from the fish whose habitats contained the several sulfonamide compounds, it could readily be seen that certain compounds exerted a retarding effect upon the multiplication of the tubercle bacilli in the bodies of the fish. The comparisons were made on the basis of the numbers of organisms per oil immersion field (980x) after averaging 100 fields. From this type of experiment the results can have no significance until the difference is rather large and quite consistent in a number of fish. For illustration, table 1 shows the results obtained in a typical control group and in groups of fish treated with sulfanilamide and sulfaguanidine, respectively. No significant effect can be ascribed to the sulfaguanidine, but it is

[2] We are greatly indebted to Dr. Joseph D. Aronson of the Henry Phipps Institute, University of Pennsylvania, for sending us this organism together with much information regarding its handling.

seen that sulfanilamide does inhibit the multiplication of the tubercle bacilli in the goldfish.

The toxicity of compounds for goldfish may also be studied on the basis of tissue concentration in so far as the solubility of a compound allows the application of this method. In this way it was determined that sulfanilamide, for example, at 300 mg. per cent in the tank water produces tissue concentrations in the fish of 100 to 185 mg. per cent with resulting death of the fish. Work of this nature is in progress to determine if this method of toxicity determination correlates with the toxicity determinations in mice and in other animals.

TABLE 1

The number of acid-fast organisms and drug concentration in the tissues of goldfish twenty-one days after infection with M. marinum

FISH NUMBER	CONTROLS	10-MG. PER CENT SULFANILAMIDE†		10-MG. PER CENT SULFAGUANIDINE†	
	Number acid-fast seen*	Number acid-fast seen*	Concentration of sulfanilamide in tissues	Number acid-fast seen*	Concentration of sulfaguanidine in tissues
			mg. per cent		*mg. per cent*
1	20 — C	1 in 2	8.0	10	7.0
2	8 — C	4	7.9	5	7.8
3	15	1 in 5	9.6	1	6.8
4	100	2	8.5	12	8.4
5	22	1 in 10	7.5	14	9.9
6	4 — C	1 in 20	11.0	3	7.2
7	12 — C	None	8.5	100	7.5
8	18 — C	5	8.7	7	8.4
9	7	3	9.1	1 in 5	8.3
10	31 — C	1 in 2	9.0	4	8.7

* = In one oil immersion field (C = many clumps seen).
† = The drug was dissolved in the water in which the fish were kept.

We have examined by this method some 40 compounds for their effects upon experimental tuberculosis. These, along with other work which is in progress, will be reported upon in the future.

SUMMARY

Common goldfish were infected intraperitoneally with *Mycobacterium marinum* and put into tanks containing low concentrations of chemotherapeutic agents (that is, sulfanilamide and others). The fish were shown to absorb the drugs from the water so that the tissues came to an equilibrium as regards the drug, the tissue concentrations being slightly below the concentration of the drugs in the water. The therapeutic effects so produced were measured by a comparison of the numbers of acid-fast organisms in smears from fish, infected three weeks previously, that were maintained in normal water and water containing drug, respectively. It was shown that certain sulfanilamide compounds exerted a retarding effect upon the multiplication of acid-fast organisms in the fish.

SUMARIO

Pececillos de colores corrientes fueron infectados intraperitonealmente con *Mycobacterium marinum* y colocados en piscinas que contenían a baja concentración elementos quimioterapéuticos (es decir, sulfanilamida y otros). Se demostró que los peces absorbían las drogas del agua, de modo que los tejidos alcanzaban un estado de equilibrio, siendo la concentración en ellos algo inferior a la alcanzada por las drogas en el agua. El efecto terapéutico así producido fué cotejado por el número de microbios ácidorresistentes en los frotes obtenidos de peces infectados tres semanas antes, que habían sido mantenidos respectivamente en agua normal y en agua medicamentada. Se demostró que ciertos sulfonamidos ejercen un efecto retardador sobre la multiplicación de los microbios ácidorresistentes en los peces.

We wish to acknowledge with thanks the technical assistance rendered by Mr. Aln T. Morpeth.

REFERENCES

(1) Rich, A. R., and Follis, R. H., Jr.: Bull. Johns Hopkins Hosp., 1938, *62*, 77.
(2) Greey, P. H., Campbell, H. H., and Culley, A. W.: Proc. Soc. Exper. Biol. & Med., 1938, *38*, 574.
(3) Birkhaug, K.: Brit. M. J., 1939, *2*, 54.
(4) Feldman, W. H., Hinshaw, H. C., and Moses, H. E.: Proc. Staff Meet. Mayo Clin., 1940, *15*, 695.

CLINICAL AND LABORATORY REPORTS

SPONTANEOUS BILATERAL PNEUMOTHORAX[1]

Case Report with Autopsy Findings

WALTER I. WERNER AND WILLIAM H. THEARLE

Though the number of cases of nontuberculous spontaneous pneumothorax reported is small, our knowledge of the subject is fairly complete. McMahon (1), Tyson (2), Kjaergaard (3) and others have reported cases and summarized the literature. Since little is found in the literature on autopsy findings, we thought it of interest to report the following case.

On September 15, 1941, a white woman, aged forty-two, was seen for the first time with a spontaneous pneumothorax on the left. Her family history was negative for tuberculosis, rheumatism, heart disease, cancer and allergy. Personal past history was irrelevant. The only point of interest in her history was an undue susceptibility to colds and bronchitis, dating back to 1937. At that time she had her first spontaneous pneumothorax on the left side. The lung reëxpanded at the end of six weeks. Since then, she has had recurring attacks of spontaneous pneumothorax, some of which occurred on the left side and some on the right. During these attacks there was low grade fever, cough, mucoid sputum, rapid pulse and breathlessness.

She came to Albuquerque in July, 1940, hoping that the dry climate of the southwest would bring about an improvement in her bronchitis.

Physical examination showed a well nourished woman (weight 130 pounds), very nervous, apprehensive looking, breathing easily. The thorax was long, slender, and the movement on the left was less than on the right. There were no bulging or visible pulsations. Over the right lung the percussion note was of good quality. Breath sounds were slightly exaggerated throughout. No râles were heard on quiet breathing or after cough. Over the left lung the percussion note was hyperresonant throughout. Breath sounds were diminished to absent throughout, anteriorly; audible but diminished, posteriorly. There were no râles, no shifting dulness or metallic tinkle. The apex beat was in the fifth interspace, 6 cm. from the midsternal line. There was no displacement of the heart. The pulse was regular, of small volume and 120 per minute. Blood pressure was 120/80. Physical examination was otherwise negative.

Fluoroscopic examination revealed the left lung to be about 60 per cent collapsed. The upper half of the left upper lobe was aerated. No fluid level was noted in either costophrenic sulcus.

Urinalysis and blood Wassermann were negative. Sputum did not contain any tubercle bacilli. Blood count: red cells, 5,100,000; white cells, 6,700; haemoglobin, 19 mg. Differential count was normal.

[1] From the Maytag Laboratories of the Southwestern Presbyterian Sanatorium, Albuquerque, New Mexico.

From the patient's report it was learned that bronchoscopic examination, done in July, 1941, had revealed a moderate amount of mucoid secretion in the bronchial tree and some chronic inflammation of the bronchial mucosa. Lipiodol studies, also made at that time, had shown a normal bronchogram.

The patient remained under medical observation, continued her work as a stenographer and her condition remained unchanged. On October 12, 1941, she suddenly became very short of breath and could not lie down. Her chest felt very full and she complained of pain in her left shoulder. These symptoms had come on rather suddenly after she had walked up a flight of stairs. Her dyspnoea increased, cyanosis developed and her condition became critical. Examination at this time revealed the breath sounds over the lower half of each lung

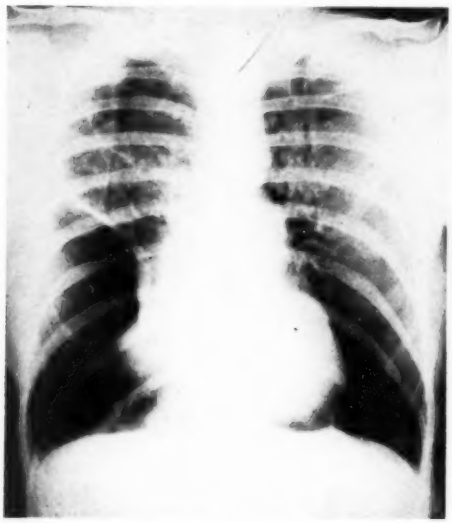


FIG. 1

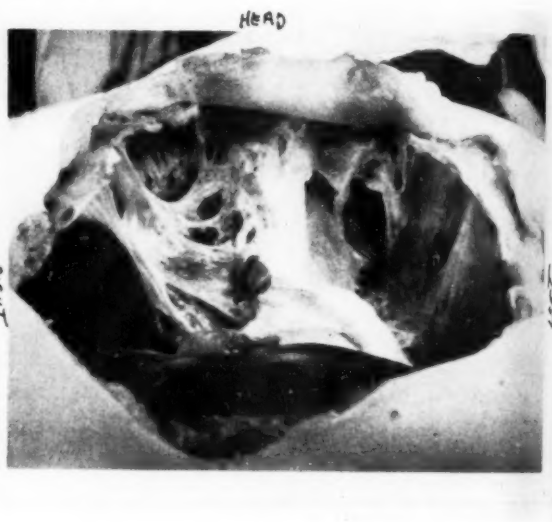


FIG. 2

FIG. 1. Bed-side film made on admission to the hospital
FIG. 2. Appearance of thorax upon removal of the breast-plate

diminished to suppressed. Her condition demanded immediate hospitalization and further studies.

An antero-posterior film of the chest (bed-side) revealed complete collapse of the right middle and lower lobes with an air pocket in the lateral area of the apex. The left lower lobe was collapsed 75 per cent. The aerated pulmonary fields showed a diffuse lacy type of infiltration which was symmetrical and of uniform density.

Patient was very dyspnoeic, apprehensive and nervous at all times. Oxygen was given constantly by nasal catheter, the average flow being 4 to 6 liters per minute. The thorax was aspirated daily, 600 to 1,200 cc. of air being withdrawn from each side, (initial intrapleural pressures +1, +6, closing −1, −4). Attempts were made to reëxpand both lungs by putting permanent catheters in each side with suction as applied by the Wangenstein method. This was not

successful. X-ray films of the chest, made on October 13, 17 and 29, revealed no change when compared with the admission film of October 12, 1941. The temperature ranged from 99 to 100°F.; pulse was 100 to 140, weak, thready; respiration was 30 to 50; blood pressure 110/90. Her condition became gradually worse, dyspnoea and cyanosis increased, cough and expectoration became very annoying and she died November 2, 1941 of respiratory failure.

Autopsy: (Only examination of the thorax permitted). On removing the breast-plate, the heart and mediastinal contents were in their normal position. The heart was smaller than its owner's fist. There was no fluid in the thoracic cavity. The lungs were almost completely collapsed, forming a small mass in the lower region of each hilum. Extending from this area and attached to the thoracic wall the upper two-thirds of the thorax were covered with silvery webb-like adhesions and emphysematous vesicles. Large pleural blebs covered the anterior surface of the right upper and the middle lobe and the left upper lobe. The lungs could be removed very easily; they were small, seemed airless, but felt rather light and feathery. The pleura was thickened over the bases of the right and left lower lobes. At no point of the pleura could tears or perforations be found. On sectioning the lungs, there was a moderate degree of emphysema throughout all lobes. This was most marked in the upper lobes. At the middle of both upper lobes some of the larger bullae were found to communicate directly with the distended alveoli. The heart was normal.

Sections made from the lung showed coalescence of the alveoli forming large emphysematous acini. There were scattered areas of round cell infiltration but no pneumonic areas. No tubercle, calcifications or other evidence of tuberculosis was noted. The pleura appeared normal.

Anatomical diagnosis: (*1*) bilateral pneumothorax, (*2*) subpleural emphysematous vesicles, (*3*) emphysema.

COMMENT

Spontaneous bilateral pneumothorax is most often the sequel of evolutive pulmonary tuberculosis or of emphysema. The latter condition may come on more or less acutely, or the onset may be slow. When emphysema comes on slowly it is termed chronic. The chronic form is associated with chronic bronchitis and other conditions in which there is much coughing over prolonged periods. There was no evidence, in the reported case, of clinical pulmonary tuberculosis on physical and roentgen ray examination together with failure to demonstrate tubercle bacilli in the sputum. Nor did the physical signs or X-ray studies give any evidence of the pulmonary emphysema.

Autopsy findings showed that, since there were no tears of the pleura present, the bilateral spontaneous pneumothorax was caused by an extensive bilateral emphysema. The larger subpleural valve vesicles occurred on the bases of the pulmonary emphysematous changes in which there was little or no scar tissue formation. Though no tears were noted in the pleura macroscopically or microscopically, such openings must have existed, at sometime or other, as the valvular pneumothorax apparently persisted until death. The rupture of these emphy-

sematous bullae is due to air entering a subpleural space more rapidly than it leaves, so that there is gradually built up a pressure sufficient to rupture the vesicle wall. As the left lung was collapsed first, this case is one of successive pneumothorax, as the right lung collapsed before the left had completely re-expanded.

CONCLUSION

A case of spontaneous bilateral pneumothorax caused by emphysema, with autopsy findings, is reported.

CONCLUSIONES

Preséntase un caso de neumotórax bilateral espontáneo producido por enfisema, con los hallazgos autópsicos.

REFERENCES

(1) McMahon, B. T.: Spontaneous bilateral pneumothorax, With report of a case and review of literature, Am. J. M. Sc., 1932, *183*, 695.

(2) Tyson, M. D., and Crandal, W. B.: The surgical treatment of recurrent idiopathic spontaneous pneumothorax, J. Thoracic Surg., 1941, *10*, 566.

(3) Kjaergaard, H.: Spontaneous pneumothorax in the apparently healthy, Acta med. Scandinav., Supplement 43, 1932.

INSPECTION OF THE LUNGS DURING RESPIRATION[1]

DIRAN YEGIAN

By means of the experiment here described, an opportunity is afforded to study, by direct examination, the mechanical factors involved in the act of respiration.

Procedure: A mouse is anaesthetized; the skin covering the chest is torn with the fingers and then stripped from the trunk of the animal. This is accomplished with practically no loss of blood (figure 1). The tissues which lie beneath the skin and envelop the organs are tenuous and, in mice three weeks old, they are so transparent that the underlying organs are seen with startling clearness. The anatomical relation of the organs of the thorax and abdomen can here be demon-

FIG. 1

strated in the undisturbed state and one may witness their coördinated to and fro movements during respiration. The experiment, moreover, permits one to observe, more accurately than has heretofore been possible, the action of the ribs, the diaphragm and the accessory muscles of respiration, as the lungs inflate and deflate. The manner in which these mechanical factors are modified by the type of breathing, (abdominal, upper thoracic and lower thoracic) can likewise be studied. By the induction of pneumothorax, one may observe the gradual collapse of the lung, and note the associated displacement and alterations in the excursion of the contiguous organs. It is surprising to see the color of the lung change from the normal pink to blue on deep anaesthesia.

The organs of the thorax and abdomen of the mouse are practically a miniature of the human, and the procedure here described has been valuable in obtaining a more precise idea of the mechanical factors participating in the act of respiration.

[1] From the New York State Hospital for Incipient Pulmonary Tuberculosis, Ray Brook, New York.

PER CENT

In *Science* of January 30, 1942, K. A. C. Elliott has a brief plea for the accurate usage of the term "per cent," which should benefit some of our contributors and readers. He points out that, for example, "a 40 per cent aqueous solution of caustic soda" may, in the author's mind, call for 40 g. of sodium hydroxide per 100 cc. of solution, which is, however, a solution containing about 30 per cent of sodium hydroxide by weight. Possibly 40 g. in 100 cc. of water is meant, which is 28.6 per cent by weight. A true 40 per cent solution is, however, 40 g. of sodium hydroxide dissolved in 60 cc. of water.

This one example suffices and further elaboration does not seem necessary here. But the final recommendation of Elliott should be repeated verbatim: *I would like to recommend that authors, when stating concentrations of solutions, should indicate exactly what is meant, by using unambiguous expressions such as* n *g. per 100 cc. solution, of* n *g. per 100 cc. solvent, or* n *g. in* m *cc. solvent.*

TREATMENT OF WAR WOUNDS OF THE THORAX

ARTHUR H. AUFSES[1]

GENERAL CONSIDERATIONS

In war wounds of the chest, the end result may be dependent not so much upon the injury itself as upon the concomitant circumstances. For instance, a wound to a civilian in a bombed city may be quickly and adequately cared for in a fully equipped hospital. On the battlefield, it may be days before a wound can receive adequate surgical care. In thoracic wounds, shock plays a great part and, if this is aggravated by external conditions, death may occur, even though the wound itself might not have been a fatal one. Furthermore, the geographic site of battle may play a great rôle in the subsequent course. The mud of Flanders was rife with tetanus and gas bacilli. On the other hand Ranson recently reported negligible infections from these organisms in chest wounds occurring in Shanghai.

The efficiency of the transport system of an army in returning the wounded to first aid stations and larger hospitals will have a great effect upon the results of severe chest wounds. For instance, Ranson had only a 10 per cent mortality in over 100 chest wounds, but he felt that this was due to the fact that poor transportation facilities prevented the more seriously wounded from reaching the base hospital.

The use of automobile and aeroplane ambulances may permit the rapid return of some wounded to the care of a trained chest team so that wounds ordinarily fatal may be operated upon successfully.

The type of missile is of great importance in the eventual outcome of the wound. Chest wounds caused by small calibre bullets will have a relatively innocuous course as compared with those wounds caused by large irregular bomb or shrapnel fragments.

The anatomy of the chest and the physiology of the respiratory system play a great rôle in the handling of thoracic wounds. The larger muscles covering the apex of the thorax tend to close off a penetrating injury of this region thereby converting it at once into a closed chest wound, the prognosis of which is much better than an open one. The lower chest has no such protective covering and large wounds of this area will probably be accompanied by all the respiratory disturbances that go with an open pneumothorax.

The soldier has probably not had any previous pulmonary disease and therefore has a pleural cavity free of adhesions. Any opening into his pleural cavity will cause a complete collapse of that lung. In the presence of a large external wound, pendulum breathing and mediastinal flutter are certain to occur. Where the visceral pleura is injured and the external opening has closed, tension pneumothorax may occur and rapidly cause death if not adequately treated. The

[1] 1085 Park Avenue, New York, New York.

early intelligent handling of such complications is of the greatest importance in the end result.

The soldier who survives his chest wound long enough to be returned to an operating room will have a good chance for life in contradistinction to the one with an abdominal wound who will probably arrive with a well developed fatal peritonitis.

World War I was the birthplace of thoracic surgery which has made tremendous advances in the succeeding two decades. With the intelligent use of the knowledge that the thoracic surgeon has acquired, many of the wounded in the present conflict will be saved and completely rehabilitated.

GENERAL THERAPEUTIC MEASURES

The shock which may accompany even a minor chest wound plays a great part in the prognosis. When the shock is not due to either haemorrhage or mechanical disturbances in respiration, it is necessary to delay operation until the general condition of the patient is so improved that he may withstand a major surgical procedure. The treatment of shock accompanying thoracic injuries will not be discussed here. It varies in no way from the methods of treating shock in general.

Where haemorrhage has been controlled and there is no response to adequate anti-shock therapy, it is advisable to postpone operation. Surgical intervention begun in the presence of severe shock will probably lead to a fatal outcome. Of course, any delay in the debridement of wounds and removal of foreign bodies increases the chances of infection, but infection in the thorax does not require as urgent care as when it occurs in the abdomen.

All patients with chest wounds should receive anti-tetanus and anti-gas therapy as well as chemotherapy. If there is no injury to the gastro-intestinal tract, warm fluids, stimulants and solid food should be given early to maintain the nutrition. Where there is anoxia, due to either mechanical causes or pulmonary infection, the inhalation of oxygen is indicated.

Blood or bronchial secretions retained in the airways and causing obstruction should be removed through the bronchoscope.

If possible, fluoroscopy and roentgenography should be used to localize foreign bodies and to give an exact picture of the intrathoracic injury. Where there is massive pleural effusion, X-ray films frequently may be of no great value.

The sulfonamides have been found to be the best therapeutic agent to combat infection and should be used liberally, both locally and systemically. They should not be superseded by any other method until such method has positively been found to be superior. Which one of the sulfonamides is to be used will have to depend in great measure upon the individual case.

WOUNDS OF THE CHEST WALL

Although, theoretically, one can have an injury to the thoracic cage without damage to the pleural cavity or thoracic organs, in actual practice such a wound is a rarity. The spinal column, ribs and sternum protect the thoracic contents

but they are not strong enough to withstand the missiles of modern warfare. Any such non-penetrating injury should be treated in the same manner as a superficial wound of any other part of the body, namely, with debridement and removal of bone splinters but with care not to enter the pleural cavity if it has not already been penetrated. Chemotherapy should be applied prophylactically and the skin may be sutured if seen before infection has set in. If infection has already occurred, debridement is indicated, followed by chemotherapy and packing.

The bony cage of the thorax is occasionally instrumental in producing bizarre injuries due to the deflection of small bullets. The points of entry and of exit do not always indicate that the missile has taken a straight course between these two sites. Cases have been reported in which the bullet has entered anteriorly and followed the course of a rib to exit posteriorly without entering the pleura.

Crushing chest wounds may occur without laceration of the skin. Multiple rib and cartilage fractures may produce marked respiratory disturbances without actual pulmonary injury. For such a "stove-in" chest, strapping of the entire hemithorax is indicated. Occasionally, a splintered rib or cartilage may cause intrapleural haemorrhage from an intercostal or internal mammary artery and require operative interference, even though there is no external wound. In like manner, perforation of the lung may occur.

WOUNDS OF THE PLEURA WITH MINOR PULMONARY DAMAGE

When pleural injuries are seen shortly after their occurrence and major surgery cannot as yet be performed, the basic therapy is to control haemorrhage and to alleviate any mechanical disturbances of respiration. In general, all efforts should be directed towards the conversion of an open pneumothorax into a closed one. This may be accomplished by packing or strapping, or the application of an occlusive superficial dressing. If possible, local chemotherapy should always be employed. If there is a bronchopleural opening, or one is suspected, it may be advisable to leave a small opening from skin to pleura to prevent the occurrence of a tension pneumothorax during transportation.

The dangers of such wounds are three: (*1*) mechanical, (*2*) haemorrhage, (*3*) infection. The first two must be controlled early, the last may be handled subsequently. As soon as major surgery can be performed, the superficial wound should be debrided and the pleural cavity thoroughly cleaned. Accessible foreign bodies should be removed. The original wound may be closed and if pleural drainage is indicated, this should be done intercostally at the most favorable site. The problem of closure or drainage of the original wound is dependent upon the degree and type of infection, the lapse of time before operation, the efficiency of the debridement and the future disposition of the patient. If it will not be possible to keep the patient under close observation for seven to ten days, it is better to drain both wound and pleural cavity. This is especially true if the wound is not a simple one, if there was a long interval before debridement and if the operation could not be thorough.

Where rapid transportation to the operating room is possible, the use of chemotherapy (both local and systemic), radical debridements and primary wound closures may result in the healing of some wounds without infection.

The management of the pleural fluid is of great importance in the treatment of thoracic wounds. Where the pleural cavity has been drained surgically, this problem will not arise unless loculation occurs. A closed thorax may be present after a penetrating injury either because of spontaneous closure at the site of entrance and exit or following primary surgical closure without drainage.

In World War I, there were many thoracic wounds caused by small bullets which sealed off their points of entry and exit, and did not cause great damage in passing through the lung tissue. Haemothorax of various degrees accompanied this type of wound, and the percentage of infections was small. Conservative therapy produced the best results.

In the present conflict, bullet wounds are less common. The lacerating wounds of large shell fragments with considerable pulmonary damage have become more frequent and will ordinarily require operative intervention in preference to conservative measures.

The treatment of pleural fluid depends upon the following factors: (*1*) general condition of patient, (*2*) nature and amount of fluid, (*3*) extent of bleeding from lung, (*4*) infection.

(*1*) *General condition of patient:* Although aspiration of the pleura for diagnostic purposes is a simple and innocuous procedure, removal of large collections should not be performed in a severely shocked patient unless the fluid itself is instrumental in producing the clinical picture. Furthermore, too rapid removal or removal of excessive amounts may be hazardous. If possible, the aspiration should be deferred until there is improvement in the general condition.

(*2*) *Nature and amount of fluid:* Fortunately, in haemorrhage into the pleural space, the blood tends to remain fluid and becomes thinned by admixture with the serous effusion which accompanies it. When this blood has originated from the lung parenchyma, it is better to leave it in place temporarily and thereby maintain the pulmonary collapse which is so vital for control of bleeding. As soon as there is evidence that bleeding has stopped, haemorrhagic collections should be aspirated and the lung permitted to reëxpand as rapidly as possible. Blood in the pleural cavity is an excellent culture medium and invites the development of infection. If still present as the lung reëxpands, it will tend to produce dense pleural adhesions which will subsequently decrease respiratory function.

If the patient with a large chest wound which has been sutured is allowed to lie upon the injured side with the wound dependent, a gradual decompression of the chest may occur by slow leakage of the pleural fluid through the wound. Where the amount of fluid in the pleura is so great that it causes cardiorespiratory distress, due to pressure on the mediastinum, it must be removed by aspiration.

Pus in the pleural cavity must be evacuated. The type of procedure will depend entirely upon the condition of the patient, the organism causing the

infection and the thickness of the exudate. Intercostal drainage may be used as a temporary measure but it will usually have to be followed by thoracotomy, at the opportune time. The presence of a bronchopleural fistula will complicate the treatment of effusions and will usually require earlier open drainage than those cases with an intact visceral pleura.

(*3*) *Extent of pulmonary haemorrhage:* Where there has been lung injury with haemorrhage into the pleura and the thorax is closed, it is not advisable to remove the pleural fluid until the bleeding from the lung has stopped. If it is necessary to remove fluid and the bleeding has not yet ceased, the pulmonary collapse should be maintained by air replacement. The amount of haemoptysis is a good indication of the status of the pulmonary bleeding and lung reëxpansion should not be attempted as long as bloody expectoration is present.

(*4*) *Infection:* Infection of the pleural cavity following chest injuries does not occur as frequently as one would expect. When it does ensue, drainage of pus is the immediate indication. If aspirations of the pleural fluid are being carried out, examination for the presence of pyogenic organisms should be made. Smears of centrifuged specimens will frequently reveal bacteria, making it unnecessary to wait for cultures. The temperature, pulse and clinical picture will all be of value in determining the onset of suppuration. The use of systemic chemotherapy as well as irrigating solutions may lessen the occurrence of pleural infections. On the other hand, they may also tend to mask the clinical picture and delay the recognition of a suppurative process. As has been stated previously, closed intercostal drainage with either suction or underwater drainage may be indicated in the early stages. As a rule, later rib resection with inspection of the pleural cavity will be necessary. At this time, foreign bodies, blood clot and fibrin masses should be removed.

If there is no bronchopleural fistula, irrigations of the infected space should be done for their mechanical value. An infected pleural space, if drained adequately and early, usually requires no antiseptic media for the eradication of the infection.

WOUNDS WITH MAJOR LUNG DAMAGE

Any wound causing marked pulmonary damage will of necessity have the same pleural complications as those with minor parenchymal injury. On the other hand, the fact that the patient has survived long enough to reach the hospital indicates that no large pulmonary vessel has been torn. At the time of operation for the thoracic wall wound, inspection of the lung and pleura should be performed and any foreign bodies easily accessible should be removed from the lung.

Areas of damaged pulmonary parenchyma may be excised or treated conservatively depending upon the extent of the lesion and the condition of the patient. Where an entire lobe has been severely macerated, immediate lobectomy may be indicated. Smaller contused areas may later become gangrenous and slough into the pleural cavity from which they can be recovered. Small inaccessible foreign bodies may be left in the lung during emergency therapy.

POSTOPERATIVE CARE

Because of the importance of diligent postoperative care after thoracic procedures, major operations should be deferred, if possible, until the wounded reaches a hospital where he can remain for a reasonable period of time. The administration of oxygen, the care of drainage and irrigation systems, the need for transfusions and the importance of careful dressings are only a few of the necessary measures which require special care.

X-ray examinations should be made frequently to discover undrained areas of suppuration, pneumonitis or atelectasis. Suitable chemotherapy should be employed and bronchoscopy done when indicated.

As soon as the emergency is over, efforts must be made to restore the cardiorespiratory system to normal. If there has been no infection, this will be relatively simple and reëxpansion of the lung will occur rapidly. Frequent aspirations of pleural fluid will hasten this process. Complete obliteration of the pleural space may be expected.

If an empyema has developed and drainage has been instituted, lung reexpansion will also occur but more slowly than in the uninfected cases with a closed hemithorax. Underwater drainage, suction, flapper valve systems (especially during transportation) as well as breathing exercises and ambulatory treatment will all aid in the reëxpansion of the lung.

Crushing of the phrenic nerve to produce a temporary diaphragmatic paralysis will be of value in the obliteration of a basal empyema space. The more rapidly pulmonary expansion occurs, the less the thoracic cage will be contracted, in the effort to obliterate the pleural cavity. The development of scoliosis will also be dependent upon the speed of healing and the avoidance of a chronic empyema.

The presence of bronchopleural fistulae will in some measure delay lung reexpansion and eventual healing. Such fistulae, as well as persistent empyema pockets, should be treated surgically as soon as the systemic and local conditions are satisfactory.

SECONDARY OPERATIVE PROCEDURES

Secondary operations will be necessary for (*1*) removal of foreign bodies, (*2*) drainage of localized intrapulmonary suppuration, (*3*) lobectomy or pneumonectomy for diffuse pulmonary suppuration, (*4*) eradication of empyema spaces, (*5*) closure of bronchial fistulae.

Foreign bodies in an infected pleural cavity will have to be removed before complete cure can be expected. In some cases, the use of the thoracoscope for this purpose may obviate the necessity for a major operation.

When foreign bodies in the lung are the seat of suppuration they should be removed. The late results of chronic pulmonary suppuration are so disastrous that every effort should be made to prevent the occurrence of this complication. By means of exact radiographic localization, foreign bodies may be removed at a secondary operation and lung abscesses drained. When this is done early and adequately, chronic suppuration, fibrosis and bronchiectasis will be avoided.

Where these sequelae cannot be avoided, lobectomy, and even pneumonectomy, should be undertaken in order to obtain a cure.

Small missiles may be permitted to remain in the lung parenchyma if they have become walled off and give no evidence of infection. Larger ones should be removed when conditions are favorable. The chances of their indefinitely remaining innocuous are small.

If empyema pockets do occur, they should be treated as early as possible by radical surgery in order to avoid scoliosis, amyloid disease and intrathoracic deformities. Such surgery may entail the use of muscle flaps, extensive rib resections or Schede type procedures. These should be performed early in order to prevent the development of chronic thoracic suppuration.

WOUNDS OF THE HEART AND PERICARDIUM

Wounds of the heart are frequently associated with injuries of other thoracic organs and in the great majority of cases are rapidly fatal. This is especially true upon the battlefield where surgical therapy can be instituted only after a considerable lapse of time. Where such injuries occur in the civilian population, early operative intervention may be a life saving measure.

Nonpenetrating injuries: Injury to the myocardium due to contusion of the chest without penetration may lead to small haemorrhages in the heart muscle which do not require surgical intervention. Continued haemorrhage into the pericardial sac from such an injury might lead to cardiac tamponade. This is amenable to surgical therapy even though the patient appears to be *in extremis*. The diagnosis and treatment of cardiac tamponade will be discussed under penetrating cardiac wounds.

Penetrating wounds: Pericardial wounds may occur without myocardial damage. If haemorrhage is not persistent, there is no need for immediate pericardial exploration. Debridement of the external wound with removal of bone fragments and drainage of the pericardial sac (if infection has set in) may be all that is necessary as an emergency measure. Foreign bodies may be retained in the pericardial sac without producing symptoms. With local and systemic use of chemotherapeutic drugs, many penetrating wounds of the chest may heal without infection. In a wound of the pericardium, persistent haemorrhage from a torn pericardial artery may occur. This requires open thoracotomy and control of the bleeding point. Such haemorrhage may occur into the pericardial sac causing tamponade or it may enter the adjoining pleural cavity through an adjacent pleural tear. In the latter case, a haemothorax will be present and active bleeding may have ceased by the time hospitalization is effected.

Some myocardial wounds may not require immediate cardiac exploration. If the missile has lodged in the heart muscle without causing a persistent haemorrhage, there is no need for immediate removal. Such an event occurs only with a small missile, and the debridement of the chest wall wound may suffice. Where the wound of entry is large, the likelihood of the occurrence of cardiac tamponade is small. Such wounds should be debrided, bone fragments removed, and the point of internal bleeding secured. Foreign bodies, if easily accessible, may be

removed. Drainage of the pericardial sac is indicated to prevent a late cardiac tamponade due either to secondary haemorrhage or serous effusion.

Where a small missile causes bleeding within the pericardial sac and the blood has no point of exit, cardiac tamponade occurs. This condition is one in which proper surgical intervention will be a life-saving measure. In cardiac tamponade, there is a gradual increase in the pressure exerted on the outside of the myocardium. The sudden increase in intrapericardial pressure first exerts itself upon the thinner auricles and prevents their dilatation thereby obstructing the venous flow into the heart chambers. Cervical veins become distended, venous pressure rises, cyanosis appears, the patient is restless and frequently assumes a sitting position with the head flexed on the chest; as the process progresses, the ventricles no longer receive their required amount of blood to discharge into the general circulation and also cannot contract efficiently. The blood pressure drops, the pulse becomes weak or absent and the apex impulse cannot be felt due to the surrounding layer of fluid. The pericardial outline is markedly enlarged.

Such a condition ends fatally unless relieved by surgical intervention. The pericardium and heart should be exposed through an incision to the left of the sternum, with removal of the third, fourth and fifth costal cartilages. After the pericardial sac is opened and the blood evacuated, the bleeding point should be ligated. If the foreign body can be easily removed, it should be extracted. If lodged in the myocardium, sutures should first be placed and made ready for tying before the missile is slowly removed. The pleura, if not already torn, may very likely be opened during the exposure of the heart. Packings should be used to seal off the pleural cavity. If a haemothorax is present, it should be evacuated and the lung reëxpanded at the end of the operation. If the external wound is closed, the pericardium should be left open for internal drainage. The closure of the wound will depend upon the amount of contamination, the efficiency of the debridement and the length of time between injury and operation. Naturally, if infection is already present, the wound should be packed. Chemotherapy is indicated in all cases.

Foreign bodies in the myocardium may be left *in situ*. After all wounds are healed, their removal may be attempted. This will depend upon the size, position and symptoms.

ABDOMINO-THORACIC WOUNDS

In view of the fact that most severe abdominal war injuries are fatal, it is evident that wounds involving both abdomen and thorax will also be fatal in a high percentage of cases. The two body cavities may be injured by separate missiles, or they may be entered by a single missile travelling either from abdomen to thorax or *vice versa*.

Approximately 10 per cent of abdominal wounds are complicated by a thoracic injury. As a rule, missiles which traverse the diaphragm from below upward produce injuries which are more serious than those which occur from above downward. In either case, the abdomen will require more urgent surgery than the thorax.

With a large diaphragmatic laceration, abdominal viscera may be found in the thoracic cavity. Whether the operative approach should be via the thorax or abdomen, or both, will depend upon the individual case. It must be remembered that injuries to the upper abdominal viscera may be repaired by a transthoracic and transdiaphragmatic approach. This is especially true of injuries to the spleen, stomach and liver.

Abdominal signs and symptoms in the presence of a chest injury are not always indicative of an intraäbdominal lesion. Injuries to the intercostal nerves, or non-penetrating wounds of the diaphragm may cause abdominal pain, tenderness and muscular rigidity. Where the point of entry is supradiaphragmatic and there is not definite evidence of abdominal penetration, the thoracic approach is indicated. The diaphragm may then be inspected.

The two sides of the body present different problems in respect to combined abdomino-thoracic injuries. On the left side, large diaphragmatic lacerations may result in herniation of stomach, colon and spleen into the chest. Their presence may lead to an erroneous diagnosis of pneumothorax. Injuries to the spleen may be sutured through a transthoracic approach, or a splenectomy may be performed. Perforations of the stomach and splenic flexure of the colon may also be repaired. On the right side, injuries to the liver may be treated through a transthoracic approach.

It must not be forgotten that intrathoracic wounds may also produce retroperitoneal injuries of the duodenum, pancreas and kidneys. The first two usually result fatally but in renal wounds, excision of the tract, control of haemorrhage and even nephrectomy for a badly macerated kidney may result in recovery.

ANAESTHESIA

The exigencies of modern warfare will determine the type of anaesthesia available for thoracic surgery. In base hospitals where anaesthesia machines and varieties of anaesthetics are available, the problem will not be far different from that arising in the well equipped civilian hospital. On the other hand, the mobility of present day fighting will not permit the use of complicated installations and large supplies of the newer anaesthetics (many of which are explosive) in the advanced surgical units.

Dependence will have to be placed upon the simplest means for anaesthesia. These include local and regional anaesthesia, intravenous barbiturates, nitrous oxide, and oxygen and ether. Chloroform, which ordinarily is used little in civilian life, may again be found to be a valuable aid in emergency thoracic surgery.

Ethylene and cyclopropane, because of their explosive qualities, will have to be abandoned. Intratracheal methods may be employed if the personnel is trained in their use. When attempted by the unskilled, they may cause more damage than they can do good. Spinal anaesthesia will probably have little use because of the danger of increasing shock.

Individual circumstances will decide the choice of anaesthetic. As a general

rule, the following factors are of importance: (*1*) rapidity of induction, (*2*) rapidity of recovery, (*3*) ease of administration, (*4*) amount of postoperative nausea and vomiting, (*5*) effect upon respiratory centre, (*6*) effect upon anoxaemia and (*7*) shock.

Positive pressure anaesthesia in surgery of the open thorax is not always necessary, but when it is needed, it is of the utmost importance. Positive pressure may be maintained by the use of a simple mask, bag and oxygen tank. This can be used in conjunction with any of the non-inhalation methods.

ACUTE PUTRID PULMONARY ABSCESS

VI. The Criteria of Cure

ARTHUR S. W. TOUROFF AND HAROLD NEUHOF[1]

In a previous communication (1) we stressed the fact that remission is common at some time during the acute stage of putrid pulmonary abscess. Thus, as drainage of the abscess into the bronchial tree becomes established the patient's fever often diminishes, and fetor and expectoration lessen and may disappear. Such amelioration of symptoms may be progressive, with termination in cure. On the other hand, improvement may be only temporary and the subsequent clinical course one of varied severity. In a recent survey of 131 patients who first came under our observation in the *subacute* and *chronic* stages of pulmonary abscess, we noted that 9 had been discharged as "cured" or "improved" during the acute stage. An analysis of the history in these instances revealed that medical treatment and observation had been discontinued during a phase of clinical remission, and that the subsequent course had been one of recrudescence of symptoms or of persistence of mild manifestations. In either event, the patients presented themselves to us for treatment in the subacute or chronic stage of the disease. (In this connection, it should be noted that we consider the acute stage of putrid pulmonary abscess to terminate at the end of six weeks of illness (2).)

A single case will suffice to illustrate the typical sequence of events in such cases:

F. T. (Hospital No. 352430), a girl five years old, was admitted to the Mount Sinai Hospital on July 7, 1933.

Six months previously, tonsillectomy had been performed under general anaesthesia at another institution. The patient was discharged the day after operation, but within the next few days she developed fever which ranged between 101° and 103°F. This continued for about one month during which time the child lost considerable weight but had no cough or expectoration. She was then readmitted to the hospital where X-ray films of the chest disclosed an abscess of the right lower lobe and an area of infiltration in the left upper lobe. For about one week the temperature varied between 102° and 105°F. but then became normal. Ten days after the first X-ray examination, another series of films revealed complete disappearance of the abscess cavity in the right lower lobe. The infiltration in the left upper lobe remained unchanged, however. In view of subsidence of fever and the disappearance of the cavity in the right lower lobe, the patient was discharged from the hospital as improved. This, in spite of the persistence of infiltration in the left upper lobe.

One week later, fever recurred and the child was readmitted to the hospital where X-ray examination of the chest revealed no change in the extent or density of the infiltration in the left upper lobe. After three weeks, during which period fever continued, films of the chest revealed cavitation within the infiltrated area. From that time on, serial roentgenograms disclosed progressive enlargement of the cavity. Following a

[1] 4 East 95th Street, New York, New York.

period of observation lasting three and a half months, the child was referred to the Mount Sinai Hospital where the diagnosis of *"healed acute putrid abscess* of the right lower lobe and *chronic putrid abscess* of the left upper lobe" was made. The subsequent course, which ended in recovery (following operation on the abscess of the left upper lobe), is not germane to the present communication.

Comment: The diagnosis of acute putrid abscess of the right lower lobe was established by X-ray examination on the first hospital admission following tonsillectomy. It is significant to note that the child had no cough or expectoration at that time. When the cavity disappeared spontaneously and fever abated, the patient was discharged from the hospital as improved, in spite of the fact that pulmonary infiltration persisted in the opposite upper lobe. As happens not infrequently, fever recurred, and several weeks later serial roentgenograms disclosed the presence of cavitation within the infiltrated area. In spite of the fact that the diagnosis of pulmonary abscess, then, was established beyond doubt, the patient was kept under observation for three and a half months and the lesion permitted to become chronic.

The foregoing case illustrates that if mild or minimal clinical manifestations are regarded as evidence of imminent or actual cure of pulmonary abscess, errors in interpretation may be committed. All observers are in agreement that, regardless of the type of treatment employed, the longer the duration of pulmonary abscess the higher the morbidity and mortality and the lower the incidence of satisfactory results. Hence, the patient who might have been subjected to effective therapy in the acute stage of the disease, but passes into the subacute or chronic stage, is placed in jeopardy. It is our purpose in this communication to present the only criteria of cure of acute putrid pulmonary abscess which we regard as satisfactory. They include a consideration not only of clinical manifestations but also of roentgenography and, at times, of bronchoscopy and bronchography. The first point to be stressed is that, regardless of subsidence or disappearance of clinical manifestations, it is a serious error to consider the patient cured unless a roentgenogram of the chest reveals disappearance not only of the abscess cavity but also of *all* pulmonary infiltration. With the patient in the erect posture, films should be made in the postero-anterior, lateral and, at times, oblique positions. The erect posture is essential for the demonstration of fluid levels within cavities and the lateral film often reveals features not demonstrable in the postero-anterior film.

As stated above, the roentgenographic criteria of cure are, first, the disappearance of cavity, and second, the disappearance of all surrounding pulmonary infiltration. It should be emphasized that *the disappearance of a fluid level alone does not necessarily signify the disappearance of a cavity.* A fluid level is produced in the roentgen film by a collection of fluid surmounted by air. If spontaneous drainage by the bronchial tree is sufficiently free, all fluid will be evacuated from the cavity, leaving only air. On the other hand, if drainage becomes impaired, fluid may fill the cavity completely. Under either cir-

cumstance, the fluid level will disappear although the cavity may remain essentially unchanged in size. The roentgen evidence of the disappearance of a cavity therefore does not consist of the disappearance of a fluid level alone. Neither is it based solely upon the disappearance of the dense shadow from within the area occupied by the abscess. However, a disappearance either of the fluid level or dense shadow, in conjunction with the absorption of the "rim" or "wall" of the abscess cavity, fulfills all requirements.

The second roentgenographic criterion of cure, namely the disappearance of all surrounding pulmonary infiltration, now will be considered. Such infiltration is due to an inflammatory reaction in the pulmonary tissue about the abscess cavity, and a subsidence of infection within the abscess is accompanied by subsidence in the extent and density of the surrounding pulmonary infiltration. At times a spread of infection from the abscess cavity into the surrounding zone of pulmonary infiltration may occur. This often results in the formation of a small locule of pus which is not distinguishable in the roentgen film from the enveloping pulmonary infiltration. Under such circumstances, if the infection within the original abscess cavity subsides, but the new loculation of pus remains, most of the pulmonary infiltration about the original cavity will disappear but a small area of tell-tale density will persist. If, on serial roentgenograms, the fresh infiltration subsequently subsides, it can be assumed that the new focus of infection has subsided. If infection persists, the pulmonary infiltration likewise persists and may begin to spread. Thus, the progress of the pulmonary infiltration noted in the roentgen film is apt to reflect accurately the course of the pulmonary infection. Accordingly, if complete subsidence of pulmonary infiltration occurs, cure may be safely assumed to have taken place. If, on the other hand, the pulmonary infiltration persists, cure cannot be assumed to have taken place *regardless of the mildness or even the absence of clinical manifestations.* In occasional cases, an abnormal shadow may be noted in the film after the patient is free of symptoms, and cavity and pulmonary infiltration have disappeared. Such shadows are noted not infrequently in cases which have been subjected to operation, and consist of clusters of clearly delineated strands between which normal pulmonary illumination is seen. We believe these represent areas of fibrosis or scarring in the region of healed cavities. Such a fibrotic scar is not to be confused with the homogeneous, more diffuse and more irregular shadow cast by areas of pulmonary inflammation. Whenever there is any question as to whether the lesion under suspicion represents an old scar or a residual inflammatory process, diagnostic bronchoscopy should be performed. If the latter is negative, it may be assumed that the shadow in question represents a scar and that cure has taken place. If, however, purulent secretion is encountered, cure cannot be considered to have occurred, regardless of the absence of clinical manifestations and the otherwise favorable appearance of the roentgen film. If secretion is minimal and is not foul, it may be assumed that infection is subsiding. However, the patient should be kept under observation either until bronchoscopy becomes negative or the diagnosis is clarified by additional studies. In these cases bronchography may be of value.

Our experience with the application of the foregoing criteria of cure of acute pulmonary abscess, both in nonoperative and operative cases, can be stated briefly. In the former, no case was discharged from observation if clinical manifestations or roentgenological evidence of pulmonary abscess existed. As a result, our cases either progressed to actual cure or were subjected to operation before the subacute stage was reached. Thus, there is not a single instance of subacute or chronic abscess of the lung among the patients who came under our observation in the acute stage of the disease and were not subjected to operation. Concerning the operative cases, the same strict criteria of cure have been applied. The persistence of even slight clinical manifestations or of limited pulmonary infiltration following operation was regarded unequivocally as evidence of persisting infection in the few instances in which they were observed. Under such circumstances, further operation was performed more promptly than might otherwise have been the case. The only additional criterion of cure in operative cases consists of a healed wound. Although an abnormal shadow in the roentgenogram usually is to be noted in the region of the open or healing wound, no operative case is to be regarded as cured until all pulmonary infiltration has disappeared.

If strict criteria of cure of pulmonary abscess are observed, the error of confusing remission with cure will not be committed. Accordingly, many patients in the relatively early stages of the disease, who ordinarily might be discharged from observation under the assumption that they have recovered, will be kept under observation and appropriate treatment applied during the period in which the best results can be achieved. Thus, regardless of the methods of therapy to be employed in this stage of the disease, if treatment proves successful, the dangers of the subacute or chronic stage of putrid pulmonary abscess will be avoided. If, finally, there is borne in mind the fact that almost all cases in the acute stage of the disease can be cured by operation (3), the imperative necessity of applying precise criteria for the recognition of a persistent infection becomes obvious.

SUMMARY

Regardless of subsidence or even complete disappearance of the clinical manifestations of acute putrid pulmonary abscess, it is a serious error to assume that recovery has taken place unless the roentgenogram reveals complete disappearance not only of the abscess cavity but also of all surrounding pulmonary infiltration. Even if the latter is only of limited extent, persistent infection must be assumed to be present.

In certain cases, following operation, abnormal shadows may be present in the former region of the abscess. These may be due to pulmonary fibrosis and scarring or to local pleuritic reaction. The absence of persistent pulmonary infection can be ruled out in such cases only by bronchoscopy and occasionally only by bronchography. When the criteria of cure have been met, complete healing can be stated to have taken place. Under such circumstances recurrence has never been noted. Thus, a generally held assumption that recurrence may

follow drainage operations for putrid pulmonary abscess can only be based upon inaccurate criteria of cure of the acute abscess.

SUMARIO

Independientemente de la atenuación o hasta desaparición completa de las manifestaciones clínicas del absceso pulmonar pútrido agudo, cométese un error grave al dar por sentado que ha tenido lugar la reposición, a menos que el roentgenograma revele completa desaparición no tan sólo del absceso, sino de toda la infiltración pulmonar circundante. Aunque la última sólo acuse una extensión limitada, hay que suponer que existe una infección persistente.

En ciertos casos, pueden presentarse después de la operación en la antigua región del absceso sombras pulmonares debidas a fibrosis y cicatrización pulmonar o a reacción pleurítica local. En estos casos sólo puede aceptarse la ausencia de infección pulmonar persistente mediante la broncoscopia y a veces sólo con la broncografía. Cuando se han cumplido los postulados de la curación, puede afirmarse que ha tenido lugar la cicatrización completa, y en esas circunstancias jamás se ha observado recurrencia. Así pues, la suposición sostenida generalmente de que pueden presentarse recurrencias tras las operaciones de drenaje en el absceso pulmonar pútrido, puede basarse únicamente en juicios inexactos en cuanto a la curación del absceso agudo.

BIBLIOGRAPHY

(1) Touroff, A. S. W., and Moolten, S. E.: The symptomatology of putrid abscess of the lung, J. Thoracic Surg., 1935, *4*, 558.

(2) Neuhof, H., and Touroff, A. S. W.: Acute putrid abscess of the lung, Principles of operative treatment, Surg., Gynec. & Obst., 1936, *63*, 353.

(3) Neuhof, H., and Touroff, A. S. W.: Acute putrid abscess of the lung, IV. Surgical treatment and results in 86 consecutive cases, J. Thoracic Surg., 1940, *9*, 439.

HAEMORRHAGE FROM THE TRACHEA, BRONCHI AND LUNGS OF NONTUBERCULOUS ORIGIN[1]

CHEVALIER L. JACKSON AND SIDNEY DIAMOND

Fifty years ago haemorrhage from the tracheobronchial tree or the lungs was regarded as being pathognomonic of pulmonary tuberculosis. With the progressive increase in the accuracy of differential diagnosis that attended the refinement of our knowledge concerning the bacteriology, the pathogenesis and the clinico-pathological features of the various bronchopulmonary diseases, it became apparent that haemoptysis not infrequently had its origin in lesions other than phthisis. To-day, while tuberculosis still continues to be responsible for more cases of blood-spitting than any other disease, the prominent rôles played by cardiovascular affections, neoplasms and other nontuberculous processes in the aetiology of bronchopulmonary bleeding are being more and more clearly recognized.

In an effort to investigate the nontuberculous bases for tracheal and bronchopulmonary haemorrhage, we made a survey of the patients with haemoptysis who were observed in the bronchoscopic clinic at Temple University Hospital from January 1, 1930 to July 1, 1941. We limited our survey to patients whose diagnostic studies were exhaustive in character and we were therefore forced to eliminate those with evident parenchymal disease in whom the precise nature of the disease was not positively established. We also eliminated those whose haemoptyses were due directly to trauma inflicted by aspirated foreign bodies and those in whom the causative lesion was demonstrated to be outside the tracheobronchial tree and the lungs. The number of patients finally selected for study was 436. Only patients with a basic work-up comprising a careful physical examination, a thorough fluoroscopic and roentgenographic survey of the chest and at least one bronchoscopy were included. In a large number, serial X-ray films of the chest were taken over a period of months or years. Follow-up bronchoscopies were performed in all patients in whom the diagnosis was uncertain at the time of the original examination. Bacteriological studies of the bronchial exudates and histological studies of pieces of tissue removed by bronchoscopy, needle aspiration, thoracoscopy or thoracotomy were made in all patients from whom specimens could be obtained. In many instances a roentgenographic and endoscopic investigation of the oesophagus and stomach was undertaken, in order to rule out the presence of a haemorrhagic focus in those organs. In several patients special haematological procedures, such as a count of the platelets and a determination of the coagulation time and the bleeding time, were carried out; the findings were invariably normal.

It must be realized that a great many patients admitted to the hospital with pulmonary bleeding are not seen by the bronchoscopist, the nature of the underlying disease being such that no indication for the direct inspection of the tracheobronchial tree is present. Included in this category are patients with cardiovascular lesions which lead to the production of chronic passive congestion or pulmonary infarction, patients with acute lobar pneumonia and patients with blood dyscrasias. This group, observed by the internist alone, represents a considerable number of patients with haemoptysis. Indeed,

[1] From the Temple University School of Medicine, Philadelphia, Pennsylvania.

in the opinion of some observers (1, 2) heart disease is second only to tuberculosis in the frequency with which it gives rise to blood-spitting.

CLINICAL FEATURES

The tracheal, bronchial and pulmonary lesions found in the 436 patients studied are shown in table 1. A limited degree of overlapping was inevitable. Patients with bronchiectasis, for instance, often had an associated focus of parenchymal pulmonary disease. Likewise, many of the patients with bron-

TABLE 1

Tracheal, bronchial and pulmonary lesions found in 436 patients with haemoptysis

NATURE OF LESION	NUMBER OF PATIENTS IN EACH AGE GROUP AT TIME OF INITIAL HAEMOPTYSIS							TOTAL NUMBER OF PATIENTS
	Less than 10 years	10 to 19	20 to 29	30 to 39	40 to 49	50 to 59	More than 60 years	
Bronchiectasis	19	25	38	19	20	15	2	138
Primary carcinoma of bronchus		1	3	9	20	34	15	82
Tracheobronchitis	4	2	21	12	12	15	8	74
Pulmonary abscess		4	15	16	9	5	2	51
No evidence of disease		2	10	14	5	3		34
Nonsuppurative pneumonitis	2		3	5	3	1	1	15
Suppurative pneumonitis		1	4	1	2	3		11
Adenoma of bronchus		3	3	3	2			11
Secondary cancer of lung				1	1	2	2	6
Lobar atelectasis		2			1	1		4
Primary carcinoma of trachea					1	1		2
Suppurating pneumoconiotic lymph node discharging into bronchus							1	1
Nonspecific granuloma of bronchus				1				1
Streptothricosis						1		1
Chondroma of bronchus						1		1
Osteoma of trachea							1	1
Dermoid cyst communicating with bronchus				1				1
Broncholithiasis							1	1
Neurofibroma involving wall of bronchus		1						1
Totals	25	41	97	82	76	82	33	436

chogenic carcinoma developed secondary suppurative processes as a result of the bronchial obstruction. In order to avoid confusion, we classified each patient according to the nature of his principal lesion. The diagnosis of bronchiectasis was based solely upon the demonstration of bronchial dilatations by contrast roentgenography. In regard to neoplastic lesions, identification of the specific type was determined by the microscopical picture of the tumor tissue. In the patients listed as having tracheobronchitis and those listed as showing no evidence of disease, the ordinary chest films were entirely normal or, at most,

revealed a questionable increase in the bronchovascular markings. There were bronchoscopic signs of chronic inflammatory disease, consisting of alterations in the color or the texture of the mucous membrane, thickening of the spurs or the presence of a bronchial exudate, in the former group; there were none in the latter. The absence of bronchiectasis in every one of the patients in the two groups was established by delineation of the bronchial ramifications with iodized oil. The diagnosis of pulmonary abscess was confined to those patients whose chest roentgenograms disclosed a well-defined vomica. Patients whose films contained changes denoting definite parenchymal involvement but no visible cavity were designated as having pneumonitis, the distinction between the nonsuppurative and suppurative varieties depending upon the character of the endobronchial exudate; in every instance, the bronchi in the involved areas were demonstrated to be of normal size by the instillation of lipiodol.

Of the total of 436 patients, 249 were men and 187 were women. The preponderance of males was due largely to the disproportionate number with primary carcinoma of the bronchus, the ratio in that group being 66 men to 16 women. There were only two other sex predilections of any consequence: of the 34 patients in whom no tracheal or bronchopulmonary disease process could be found, 22 were women; of the 11 patients with adenoma of the bronchus, all but one were women.

In all 4 patients in whom lobar atelectasis was associated with the occurrence of bronchopulmonary haemorrhage it was the right middle lobe that was involved. Each of these patients gave a history of several attacks of haemoptysis shortly before admission. In one the bronchoscopic removal of a blood clot occluding the orifice of the right middle lobe bronchus was followed in a few days by complete reaeration of the atelectatic area, strongly suggesting that the lobar collapse bore no significant relation to the production of the bleeding but was merely a consequence of the intrabronchial retention of some of the blood. In the other 3, varying quantities of mucopurulent material were aspirated from the affected lobe but no sign of haemorrhage could be discerned on repeated bronchoscopic examination; several weeks were required for the attainment of reëxpansion in each patient.

Of the 6 patients with haemoptysis who were found to have metastatic cancer of the lung, carcinoma of the thyroid was the primary site in 2, carcinoma of the breast in one, hypernephroma in one and endothelioma of the kidney in one. In one patient the location of the original tumor could not be ascertained because permission for only a limited autopsy was granted.

The relative haemorrhagenic tendencies of the different nontuberculous lesions, as observed at Temple University Hospital, are extremely interesting. Of the patients with bronchial adenoma encountered by us since 1930, expectoration of blood was present in 100 per cent. On the other hand, it occurred in only 42 per cent of those with pulmonary abscess, 35.2 per cent of those with primary carcinoma of the bronchus and 28.2 per cent of those with bronchiectasis. That haemoptysis is one of the cardinal symptoms of adenoma of the bronchus has been pointed out by numerous observers (3, 4, 5, 6, 7, 8); its in-

cidence among our patients with adenoma, although striking, was not extraordinarily high in comparison with that present in other series of appreciable size. Likewise, the incidence of haemorrhage in our patients with pulmonary abscess and in those with bronchogenic carcinoma was similar to that noted in most clinics. The proportion of bronchiectatic patients who had haemoptysis, however, was somewhat smaller in our series than has generally been observed elsewhere. Perry and King (9) report the occurrence of haemorrhage in 37 per cent of their patients, Fletcher (10) in 38 per cent and Warner (11) in 45 per cent. In the experience of other investigators (12, 13) the incidence has been even higher. Vinson (14) has found the relative frequency of haemoptysis among bronchiectatic patients nearly twice as great as that among tuberculous patients.

It will be noted that, of the 66 patients in our group who had their initial attack of blood-spitting before they were twenty years of age, 44 (67 per cent) had bronchial dilatations. Boyd (15) has called attention to the fact that haemoptysis is seen more often in bronchiectasis than in any other bronchopulmonary disease of childhood. Nevertheless, the actual incidence of haemorrhage among children with bronchiectatic disease is distinctly smaller than it is among adults. In a recent study (16) of childhood bronchiectasis in our clinic, only 20 per cent of the patients were found to have expectorated blood.

Most of the patients in our series suffered from a chronic cough, which was particularly apt to be present during the episodes of blood-spitting, but 93 had no cough at all. Of these 93 patients, 22 were found to have tracheobronchitis, 21 had no demonstrable disease, 18 had bronchiectasis, 13 had bronchogenic carcinoma, 6 had nonsuppurative pneumonitis, 4 had bronchial adenoma, 3 had secondary pulmonary cancer, 2 had suppurative pneumonitis, one had a pulmonary abscess, one had lobar atelectasis, one had primary carcinoma of the trachea and one had broncholithiasis. Our 18 patients with the truly dry haemorrhagic type of bronchiectasis, described by Bezançon (17) and his coworkers, represented 3.7 per cent of the total number of patients with bronchiectasis seen at Temple University Hospital and 13 per cent of the bronchiectatic patients who had haemoptysis. In a group of 400 patients with bronchial dilatations reviewed by Perry and King (9), expectoration of blood was the sole symptom in 2.75 per cent; in Warner's (11) series, it occurred as the only manifestation in 2 per cent. It is interesting to observe that in but one of our patients with dry bronchiectasis did haemoptysis occur before he was ten years of age.

As illustrated by the figures in table 2, the ordinary chest roentgenograms were essentially normal in 32 per cent of our patients. The sex distribution among these patients was approximately equal, there being 72 women and 68 men in the group. It will be observed that only 20 per cent of the total number had bronchial dilatations and that only 2 per cent had neoplasms. The paucity of statistical data in the literature precludes any precise comparison of our findings in this regard with those of other investigators. Arbuckle (18) has reported that bronchiectasis with ulceration has been the causative disease

in most of the cases of haemorrhage of obscure origin in his clinic and McGibbon and Baker-Bates (19), Roberts (20) and others (21, 22) have cited isolated instances of patients with normal physical and roentgenographic findings who had tumors or other demonstrable lesions of the tracheobronchial tree, but detailed analyses of large series of cases have not been recorded.

Mention is made occasionally in the literature of repeated bronchopulmonary haemorrhage in women as being a manifestation of vicarious menstruation (23, 24). In only 3 of the women in our series, however, was there a suggestion of anything other than a coincidental relationship between the menstrual cycle and the occurrence of haemoptysis. In one, who had no visible tracheobronchial or pulmonary lesion, all of the episodes of blood-spitting were concurrent with her menses and during a number of them, tiny haemorrhagic spots made their appearance in the buccal mucosa. Another woman, who also had no demon-

TABLE 2

Tracheal and bronchial lesions found in 140 patients with haemoptysis whose ordinary chest roentgenograms were normal in appearance

NATURE OF LESION	NUMBER OF PATIENTS IN EACH AGE GROUP AT TIME OF INITIAL HAEMOPTYSIS							TOTAL NUMBER OF PATIENTS
	Less than 10 years	10 to 19	20 to 29	30 to 39	40 to 49	50 to 59	More than 60 years	
Tracheobronchitis	4	2	21	12	12	15	8	74
No evidence of disease		2	10	14	5	3		34
Bronchiectasis	3	4	3	6	6	6		28
Adenoma of bronchus					1			1
Primary carcinoma of trachea					1			1
Osteoma of trachea							1	1
Broncholithiasis							1	1
Totals	7	8	34	32	25	24	10	140

strable bronchopulmonary disease, suffered from metrorrhagia and her frequent haemoptyses were invariably accompanied by some degree of vaginal bleeding. The third woman had a bronchial adenoma and, although her attacks of blood-spitting were for the most part unrelated to the time of her vaginal flow, the most severe ones were the few which took place during her menstrual periods.

Nearly all of our patients had more than one attack of haemoptysis and in 55 (12.6 per cent) at least one of the attacks was marked by the expectoration of a large quantity of blood, ranging from several ounces to more than a quart. As can be seen in table 3, more than one-third of the patients who had massive haemorrhages were in the bronchiectatic group. Yet, in not a single instance did haemoptysis in a patient with bronchiectasis terminate fatally, a fact that corroborates the observations of Goldman (24) and of Perry and King (9) that, despite the frequent occurrence of bronchopulmonary bleeding in bronchiectasis, haemorrhage in patients with that disease rarely has an immediately fatal

outcome. Three of the patients in our series did die in the midst of a copious haemorrhage but each had a nonbronchiectatic pulmonary abscess, with no evidence of bronchial dilatation.

The advisability of performing an endoscopic examination for diagnosis while frank bronchopulmonary bleeding is in progress had been the subject of considerable controversy. Some observers believe that in many cases it is possible to detect the source only when the bleeding is active and, therefore, delay in the direct inspection of the tracheobronchial tree is unwarranted. Others feel that nothing is to be gained by bronchoscoping a patient during or immediately following a hemorrhage. We are inclined to agree with the latter point of view. When the bleeding is so mild that it is evidenced only by a slight streaking of the patient's sputum, it offers no contraindication to the introduction of an endoscopic tube, even in the midst of the haemorrhagic episode. The situa-

TABLE 3

Tracheal, bronchial and pulmonary lesions found in 55 patients who had one or more massive haemoptyses

NATURE OF LESION	NUMBER OF PATIENTS IN EACH AGE GROUP AT TIME OF INITIAL HAEMOPTYSIS							TOTAL NUMBER OF PATIENTS
	Less than 10 years	10 to 19	20 to 29	30 to 39	40 to 49	50 to 59	More than 60 years	
Bronchiectasis	5	3	7	2	1	1	1	20
Pulmonary abscess			4	2	4			10
Tracheobronchitis	1			4	2	2		9
No evidence of disease		2	2	2	1			7
Nonsuppurative pneumonitis			2			1		3
Primary carcinoma of bronchus					1	2		3
Adenoma of bronchus		1		1				2
Suppurative pneumonitis			1					1
Totals	6	6	16	11	9	6	1	55

tion is far different in the case of larger haemorrhages, however. Every bronchoscopist who has at some time endeavored to advance a bronchoscope through a lumen which is being continuously filled with blood will attest to the fact that a thoroughly satisfactory diagnostic examination under such circumstances is virtually impossible. The passage of a bronchoscope a few hours after haemoptysis of any appreciable degree, albeit free from the technical difficulty created by the presence of active haemorrhage, is fraught with the danger of its precipitating fresh bleeding. When frank haemoptysis occurs, therefore, it is best to postpone endoscopic study until several days have elapsed since its cessation. If the bleeding lesion is located in an accessible bronchus, it will in all likelihood still be clearly visible at that time.

In only 109 (25 per cent) of our 436 patients could a haemorrhagenic focus actually be seen on direct inspection of the tracheobronchial tree. It will be

noted in table 4 that nearly all of the neoplasms causing haemoptysis arose in major bronchi and thus were readily apparent endoscopically. In only a negligible number of inflammatory lesions, on the contrary, was it possible to detect a definite bleeding point. Of the 5 patients with tracheobronchitis who had visible tracheobronchial ulceration, a solitary ulcer was present in the trachea in one and in the left main bronchus in each of 3 others; in the fifth patient multiple erosions were found in various parts of the trachea and both bronchi. In the patients with bronchiectasis, pulmonary abscess and nonsuppurative pneumonitis listed in table 4, all of the visible ulcers were situated in the bronchi, none in the trachea. The findings in our patients suggest that

TABLE 4

Lesions found in 109 patients with haemoptysis in whom site of bleeding could be seen at bronchoscopy

NATURE OF LESION	NUMBER OF PATIENTS
Primary carcinoma of bronchus	73
Adenoma of bronchus	11
Bronchiectasis, with visible ulceration of bronchial mucous membrane	6
Tracheobronchitis, with visible ulceration of tracheal or bronchial mucous membrane	5
Primary carcinoma of trachea	2
Nonsuppurative pneumonitis, with visible ulceration of bronchial mucous membrane	2
Pulmonary abscess, with visible ulceration of bronchial mucous membrane	1
Metastatic hypernephroma involving wall of bronchus	1
Suppurating pneumoconiotic lymph node discharging into bronchus	1
Nonspecific granuloma of bronchus	1
Streptothricosis	1
Chondroma of bronchus	1
Osteoma of trachea	1
Dermoid cyst communicating with bronchus	1
Broncholithiasis	1
Neurofibroma involving wall of bronchus	1
Total	109

tracheal ulceration is an extremely rare cause of haemoptysis, but Soulas (25) has reported an impressive series of cases in which the bleeding apparently originated in inflammatory mucosal erosion of the trachea.

In a number of cases recorded in the literature, the haemorrhage has been ascribed to vascular abnormalities in the walls of the trachea or the bronchi. Bleeding telangiectases have been described by various authors, Gerlings (25) employing the term "venectasies" to depict the condition that is present. Varicose veins have been cited by McGibbon and Baker-Bates (19) and by Wood (26) as constituting the aetiological factor in sporadic instances of haemoptysis. In our experience, local vascular lesions have not been prominent

features in the production of tracheobronchial haemorrhage. Six of the patients in our series presented small areas in the mucous membrane of the trachea or the large bronchi that contained what appeared to be tufts of dilated capillaries, but at no time was there the slightest endoscopic evidence of recent or active bleeding in any of these areas. Varicose veins were not observed at tracheoscopy or bronchoscopy in any of our patients.

DISCUSSION

The necessity for painstaking, detailed diagnostic study in patients with haemoptysis cannot be stressed too strongly. Short cuts and diagnosis by inference are to be condemned, for they are beset with too many pitfalls to insure any great degree of accuracy. Anamnesis is extremely important, especially in regard to the presence of accompanying symptoms. Goldman (24) has pointed out that differentiation between bronchopulmonary haemorrhage and haematemesis is usually not difficult: blood from the lower respiratory tract is characteristically frothy, is bright red in color and is apt to be mixed with bronchial secretion or exudate; whereas blood from the stomach ordinarily is dark and is often mixed with particles of food. In cases of massive haemorrhage, he observes, pallor and loss of consciousness are likely to precede a haematemesis; while in episodes of profuse bronchopulmonary bleeding the blood almost invariably is expectorated before signs of acute blood loss appear. Should there be the slightest suspicion that haematemesis has occurred, however, a thorough investigation of the esophagus, stomach and duodenum is indicated. Careful physical examination must not be neglected; it may be the only means whereby we can localize the site of bleeding as being above or below the glottis. Unless an obviously haemorrhagic lesion is present in the nasal, oral or pharyngeal cavities or in the larynx, we must assume that the source of the blood is subglottic. Myerson (27) estimates that in more than 95 per cent of cases of blood-spitting not associated with vomiting or regurgitation, the blood is brought up from the lower respiratory tract. He calls attention to the fact that far too much emphasis has been placed upon varicose veins at the base of the tongue as haemorrhagic foci. In his experience, identical with ours, tongue base varices have not been found responsible for a single case of haemoptysis.

The history and the physical findings may suffice to establish the lower respiratory tract as the source of the bleeding, but precise localization and identification ot the causative lesion are dependent upon supplementary procedures. A comprehensive fluoroscopic and roentgenographic examination of the chest, including planigraphy and bronchography when indicated, is in order in every case of haemoptysis. The same is true of bronchoscopy, except in cases wherein a cardiovascular, haemopathic or tuberculous basis for the haemorrhage can be clearly demonstrated. A point to be remembered is that serial X-ray films and serial endoscopies will sometimes serve to clarify a picture whose significance is obscure when the patient is first examined. Other essential parts of the diagnostic program are histological examination of tissue specimens and bac-

teriological examination of material aspirated at bronchoscopy. We should not lose sight of the fact that tuberculosis is still the foremost cause of bronchopulmonary haemorrhage and that the disease masquerades under many and varied guises. An inquiry into the cause of a patient's haemoptysis must be considered incomplete until the tuberculous or nontuberculous nature of the underlying lesion has been established beyond question.

The findings in our patients indicate that haemoptysis of nontuberculous origin has its foundation in an inflammatory process much more often than in a neoplasm. Less than 25 per cent of the patients in our series had new growths. As a matter of fact, bronchiectasis alone was responsible for more cases of haemorrhage than were all of the tumors, benign and malignant, primary and secondary. In contrast to the frequency with which it is seen in tuberculosis, bronchogenic spread incident to haemorrhage appears to be exceedingly rare in nontuberculous diseases. In none of our patients could the distant extension of an inflammatory process be directly attributed to the occurrence of bronchopulmonary bleeding. It is interesting to note that of our 138 bronchiectatic patients who had repeated haemoptysis, the bronchial dilatations remained limited to one side in 92 and to a single lobe in 57.

It has been pointed out by Rogers (28), Hruby and Sweany (29) and others (30, 31, 32) that haemoptysis is rarely an early symptom in bronchial carcinoma. Confirmatory evidence is offered by the findings in the patients seen in our clinic. In only 4 (1.8 per cent) of those with malignant tumors of the bronchus was expectoration of blood the initial manifestation. Of the 82 who had haemoptysis, definite changes in the chest roentgenogram were already present in every one at the time of his admission to the hospital. Moreover, in only one of these 82 patients was pneumonectomy feasible; in the remainder who came to operation the lesion was found to be too far advanced to permit surgical cure. Tuttle and Womack (33) have shown that tumors of the major bronchi are more likely to give early symptoms, to extend slowly and to be amenable to operative removal than are those which arise in other parts of the bronchial tree. When we consider that the neoplasm was situated in one of the larger, endoscopically accessible bronchi in fully 90 per cent of our 82 patients with haemorrhagenic bronchial cancer, the outlook becomes distinctly brighter than it is apt to appear at first glance. It is quite obvious, however, that, if a successful therapeutic result is to be achieved, bronchoscopy must be done early in the course of the disease, before the symptoms have reached the haemoptysic stage, in order that we may recognize the carcinoma in its very incipiency.

We are faced with the fact that, despite our application of all the modern methods of diagnostic approach, the precise cause of haemoptysis must remain a matter of conjecture in a large proportion of the cases. In our series, the patients with tracheobronchitis, other than the few in whom mucosal ulceration could be seen endoscopically, and the patients with no evidence of disease fall into this category. Wessler and Jaches (34) have advanced the theory that sclerosis of the small vessels may be responsible for many bronchopulmonary haemorrhages of obscure aetiology. Myerson (27) has suggested that the pres-

ence of an exposed blood vessel in the wall of a peripheral bronchus may be a significant factor. It seems to us that the likelihood of existence of ulcerative lesions in the segmental bronchi and their branches merits serious consideration. Drawing an analogy with the condition prevalent in bronchiectasis, we might point out that bronchial dilatations, as a rule, are found not in the bronchoscopically accessible bronchi but in the more distal portions of the bronchial tree. Indeed, in a large number of patients with dry bronchiectasis that part of the tracheobronchial tree which can be directly visualized appears entirely normal. The rarity of ulcerative inflammatory lesions in the larger bronchi, therefore, in no wise detracts from the possibility of their occurrence in bronchi too small to be explored endoscopically. Whatever the exact nature of the causative lesion may be in these cases, our inability to establish its site as being in a particular segment or lobe, or even in one or the other lung, precludes the use of radical therapeutic measures, such as the removal of part or all of a lung, which might be applicable in the case of other bleeding bronchopulmonary disease processes. Fortunately, the prognosis for life in these patients is excellent, for, although the haemorrhages are prone to recur over a period of many years and at times may be so profuse that they cannot but occasion a good deal of alarm, experience has taught us that the likelihood of their resulting in the death of the patient is extremely small.

SUMMARY

The results of diagnostic study in 436 nontuberculous patients with tracheal, bronchial and pulmonary bleeding were analyzed. Only patients seen by the bronchoscopist were included in the analysis. Inflammatory processes were found responsible for the haemorrhage in the majority of the cases, the most common aetiological agent being bronchiectasis. Bronchial dilatations were demonstrated in more than one-third of the patients who had massive haemoptyses and in fully two-thirds of those whose initial attacks of blood-spitting occurred before they were twenty years of age. Nevertheless, in a study of the relative haemorrhagic tendencies of various nontuberculous bronchopulmonary lesions, it was found that expectoration of blood occurred actually in a smaller percentage of bronchiectatic patients than in patients with primary carcinoma of the bronchus, in those with pulmonary abscess and in those with bronchial adenoma. Fatal haemoptysis occurred in but 3 of the patients in the series, each of whom had a pulmonary abscess.

A haemorrhagic focus could be seen on bronchoscopic examination in 25 per cent of the patients. Nearly all of the neoplasms causing haemoptysis arose in major bronchi and thus were readily apparent endoscopically. In only a negligible number of inflammatory lesions, however, was it possible to detect a definite bleeding point. There was no endoscopic evidence of recent or active bleeding from a vascular lesion in the tracheobronchial tree in any of the patients.

The precise cause of the haemoptysis could not be determined in nearly one-fourth of the patients. These were patients in whom no parenchymal disease was demonstrable on roentgenography and no bleeding point evident on bron-

choscopy. The likelihood of existence of ulcerative lesions in the smaller bronchi of these patients must be considered.

Despite the fact that in fully 90 per cent of the patients with haemorrhagic bronchial cancer the neoplasm was situated in one of the larger, bronchoscopically accessible bronchi and that bronchoscopy was performed in these patients soon after the occurrence of the first episode of blood-spitting, the process was found to be too far advanced to permit surgical cure in all but one. Taking into consideration the fact that expectoration of blood is the initial manifestation of carcinoma of the bronchus in only a very small percentage of the patients, it is obvious that bronchoscopy must be done and the diagnosis made early in the course of the disease, before the symptoms have reached the haemoptysic stage, if a successful therapeutic result is to be achieved in these cases.

SUMARIO

Analízase el resultado del estudio diagnóstico de 436 sujetos no tuberculosos en que había hemorragia traqueal, bronquial o pulmonar, comprendiendo exclusivamente enfermos observados por el broncoscopista. En la mayoría de los casos la causa de la hemorragia residía en procesos inflamatorios, siendo el más común bronquiectasia. Descubriéronse dilataciones bronquiales en más de la tercera parte de los enfermos que tenían hemoptisis masiva, y por lo menos dos terceras partes de aquéllos cuyos ataques hemotípsicos se iniciaron antes de cumplir veinte años. Sin embargo, en un estudio de las tendencias hemorrágicas relativas de varias lesiones broncopulmonares no tuberculosas, observóse que la expectoración de sangre se presentaba en un porcentaje más pequeño de bronquiectáticos que en los casos de carcinoma primario del bronquio o con absceso pulmonar o adenoma bronquial. Sólo en tres de los enfermos de la serie sobrevino una hemoptisis letal, y en los tres había absceso pulmonar.

En 25 por ciento de los enfermos podía observarse con la broncoscopia un foco hemorrágico. Casi todas las neoplasias que provocaban hemoptisis se originaban en los bronquios mayores, de modo que era fácil observarlas endoscópicamente, pero sólo en un número menospreciable de lesiones inflamatorias fué posible distinguir un punto sangrante bien definido. En ninguno de los enfermos descubriéronse signos endoscópicos de hemorragia reciente o activa procedente de una lesión vascular en el árbol traqueobronquial.

Casi en la cuarta parte de los enfermos no pudo determinarse con precisión la causa de la hemoptisis. Hubo enfermos en que la roentgenografía no distinguió afección del parénquima, y la broncoscopia no reveló puntos sangrantes. Hay que considerar la probable existencia de lesiones ulceradas de los bronquios más pequeños en estos enfermos.

A pesar de que en 90 por ciento de los casos de cáncer bronquial hemorrágico la neoplasia estaba situada en uno de los bronquios mayores, broncoscópicamente accesibles, y que se practicó la broncoscopia en estos enfermos poco después de sobrevenir el primer episodio hemoptísico, el proceso resultó demasiado avanzado para permitir la curación quirúrgica en ninguno de ellos, con una excepción. Tomando en consideración el hecho de que la expectoración

de sangre constituye la manifestación inicial del carcinoma bronquial sólo en un porcentaje pequeñísimo de los enfermos, es manifiesto que hay que verificar la broncoscopia y que hacer el diagnóstico tempranamente, antes de que los síntomas alcancen el período hemoptísico, si va a obtenerse éxito terapéutico.

REFERENCES

(1) French, H.: An index of differential diagnosis of main symptoms, William Wood and Co., Philadelphia, 1912, p. 320.

(2) Lord, F. T.: Cited by Lemon, W. S.: The significance of hemoptysis in the diagnosis of thoracic disease, Canad. M. A. J., 1930, *22*, 639.

(3) Kramer, R.: Adenoma of the bronchus, Ann. Otol., Rhin. & Laryng., 1930, *39*, 689.

(4) Wessler, H., and Rabin, C. R.: Benign tumors of the bronchus, Am. J. M. Sc., 1932, *183*, 164.

(5) Jackson, C. L., and Konzelmann, F. W.: Bronchoscopic aspects of bronchial tumors; with special reference to so-called bronchial adenoma (reports of twelve cases), J. Thoracic Surg., 1937, *6*, 312.

(6) Jackson, C., and Jackson, C. L.: Tumors of bronchi and lungs, The Cyclopedia of Medicine, F. A. Davis Co., Philadelphia, 1933, vol. 8, p. 418.
Benign tumors and tumor-like conditions in the tracheobronchial tree, Am. J. Surg., 1938, *42*, 275.

(7) Goldman, A.: Polypoid bronchial tumors; with special reference to bronchial adenomata, California & West. Med., 1940, *53*, 123.

(8) Goldman, A., and Stephens, H. B.: Polypoid bronchial tumors, with special reference to bronchial adenomas, J. Thoracic Surg., 1941, *10*, 327.

(9) Perry, K. A., and King, D. S.: Bronchiectasis; a study based on follow-up of 400 patients, Am. Rev. Tuberc., 1940, *41*, 531.

(10) Fletcher, E.: Bronchiectasis; a study of 100 proved cases, J. Thoracic Surg., 1935, *4*, 460.

(11) Warner, W. P.: Factors causing bronchiectasis; clinical application to diagnosis and treatment, J. A. M. A., November 23, 1935, *105*, 1666.

(12) Hedblom, C. A.: Pathogenesis, diagnosis and treatment of bronchiectasis, Surg., Gynec. & Obst., 1931, *52*, 406.

(13) Marcy, C. H.: Bronchiectasis, Internat. Clin., 1937, *1*, 144.

(14) Vinson, P. P.: Pulmonary hemorrhage in cases of pulmonary tuberculosis, chronic bronchiectasis and mitral stenosis, Ann. Otol., Rhin. & Laryng., 1928, *37*, 675.

(15) Boyd, G. L.: Bronchiectasis in children, Canad. M. A. J., 1931, *25*, 174.

(16) Diamond, S., and Van Loon, E. L.: Bronchiectasis in childhood, J. A. M. A., 1942, *118*, 771.

(17) Bezançon, F., Weil, M. P., Azoulay, R., and Bernard, E.: Dry hemoptysic type of bronchiectasis, Bull. Acad. de méd. Paris, 1924, *91*, 100.

(18) Arbuckle, M. F.: Pulmonary hemorrhage studied and treated by the bronchoscopist, Ann. Otol., Rhin. & Laryng., 1936, *45*, 1114.

(19) McGibbon, J. E. G., and Baker-Bates, E. T.: Direct bronchoscopic investigation in haemoptysis without physical or radiological manifestations, Brit. M. J., January 16, 1937, *1*, 109.

(20) Roberts, J. C.: A case of bronchostaxis, Ibid., May 22, 1937, *1*, 1069.

(21) Morlock, H. V., and Pinchin, A. J. S.: Haemoptysis: a note on pathology and treatment, Ibid., October 27, 1934, *2*, 762.

(22) Gerlings, P. G.: Bronchoscopy in haemoptysis, J. Laryng. & Otol., 1936, *51*, 508.

(23) Chapman, R. S.: Unusual type of vicarious menstruation, Brit. M. J., June 23, 1928, *1*, 1065.

(24) Goldman, A.: Diagnosis and treatment of pulmonary bleeding, M. Clin. North America, 1936, *20*, 483.

(25) SOULAS, A.: Les hémorragies trachéales, Ann. de méd., 1930, *28*, 382.
(26) WOOD, F. G.: The value of radiology in the elucidation of haemoptysis, Brit. M. J., July 30, 1938, *2*, 211.
(27) MYERSON, M. C.: Bronchoscopic aspects of hemoptysis, Ann. Otol., Rhin. & Laryng., 1936, *45*, 1101.
(28) ROGERS, W. L.: Primary cancer of the lung; a clinical and pathological study of 50 cases, Arch. Int. Med., 1932, *49*, 1058.
(29) HRUBY, A. S., AND SWEANY, H. C.: Primary carcinoma of the lung; with special reference to incidence, early diagnosis and treatment, Ibid., 1933, *52*, 497.
(30) HOCHBERG, L. A., AND LEDERER, M.: Early manifestations of primary carcinoma of the lung, Ibid., 1939, *63*, 80.
(31) JENKINSON, E. L., AND HUNTER, A. F.: Bronchiogenic carcinoma; a diagnostic enigma, J. A. M. A., December 30, 1939, *113*, 2392.
(32) DIAMOND, S.: Clinical diagnosis of primary carcinoma of the lung, Am. Rev. Tuberc., 1941, *43*, 713.
(33) TUTTLE, W. C., AND WOMACK, N. A.: Bronchiogenic carcinoma: a classification in relation to treatment and prognosis, J. Thoracic Surg., 1934, *4*, 125.
(34) WESSLER, H., AND JACHES, L.: Clinical roentgenology of diseases of the chest, Southworth Publishing Co., Troy, New York, 1924, p. 160.

TREATMENT OF PULMONARY TUBERCULOSIS BY CADMIUM SULPHIDE[1]

B. A. DORMER, F. J. WILES AND J. FRIEDLANDER

Cadmium therapy for pulmonary tuberculosis was first suggested by Walbrum (1) who experimented with numerous heavy metals in tuberculous animals. Cadmium, among others, was considered to have a definite inhibitory effect. In 1937, Lund (2) treated 38 cases with cadmium diuretin and claimed that the sputum became negative in 24. Maigre and Reymier (3) treated 6 cases with an iodine-gold-cadmium compound and all the cases were improved.

In 1937 Heaf (4) experimented with a number of cadmium compounds and selected cadmium sulphide as the most suitable for therapeutic use. He administered this intramuscularly as a 1 per cent emulsion in olive oil. He treated 27 cases and claimed clinical improvement in 21, conversion of the sputum in 13 and radiological improvement in 11. He gave weekly doses varying from 1 to 3 cc. and a total dosage varying from 6 to 84 cc. The average total dosage was 38 cc.

In 1938 Cornwall (5) treated 40 cases, of whom 36 had a bad prognosis. In this unfavourable group 8 showed clinical improvement. The usual dosage was 1 cc. twice weekly with a total dosage of 30 cc.

In 1939 Roberts (6) reported briefly on a series of 32 cases treated with 0.5 cc. twice weekly. The total dosage was not mentioned. He had no remarkable results but advocated an extended trial.

The purpose of this paper is to describe a series of 26 cases treated with 1 per cent cadmium sulphide in olive oil. Six cases were European and the remainder either Indian or Cape Coloured. Their ages varied from sixteen to sixty-four years with an average of thirty-four years. Half the cases had moderately advanced disease and the remainder were far advanced. Fourteen cases showed cavitation on the X-ray plate, but in 3 of these the cavity was early and thin-walled. Twelve cases had infiltration without cavitation.

The dosage was as follows:

1 cc. once weekly— 2 cases
2 cc. once weekly— 4 cases
2 cc. twice weekly—16 cases
3 cc. twice weekly— 4 cases

The total dosage varied from 20 cc. to 144 cc. with an average total dosage of 74 cc. (About 10 other cases were treated but in none of them did the dosage exceed 12 cc., and this was not considered sufficient to warrant their inclusion in this series.)

All cases were on routine sanatorium treatment. One case with massive disease on the left and scattered disease on the right had a pneumothorax. Four cases with unilateral disease had a phrenicectomy.

[1] From the King George V Hospital for Tuberculosis, Durban, South Africa.

Toxic symptoms: In 7 cases a transient albuminuria occurred but in none of them did it last longer than two weeks. Treatment was not stopped on account of this. In one case a rash occurred on the hands and arms. This consisted of red, scaly, oval spots from one-fourth to one-half inch long. They were widely separated—about fifteen in all. Treatment was discontinued and the rash disappeared after a few weeks. Only 27 cc. had been given when the rash appeared so it probably had no connection with the drug.

In 2 cases it was thought that the cadmium may have had a deleterious effect. In each case during and for some time after the course of injections the general condition and weight were declining. Yet about three months after the termination of treatment the weight began steadily to increase and the general condition improved considerably. The dosage in these 2 cases was 51 cc. and 144 cc., respectively. While there is no proof, the possibility that cadmium was definitely harmful in these 2 cases cannot be excluded.

Results: All cases were carefully controlled with X-ray and sputum examination and blood sedimentation (Cutler's method). The sputum was positive in all cases and in no case did it become negative. Four cases died during treatment.

Of the remaining 22 cases, 9 showed an increase in weight of more than two pounds, 5 remained about the same and 8 lost weight. This result is no better than would be expected in a group of sanatorium patients and any improvement cannot be attributed to cadmium.

Apart from weight, only one case showed definite improvement. In this case a fairly satisfactory pneumothorax was obtained on the left side, but there was also scattered disease in the right lung and this showed marked clearing on the X-ray plate while the sedimentation rate fell from 26 mm. to 16 mm. We consider, however, that the progress made by this patient was fully accounted for by the control of the massive disease in the left lung by collapse therapy.

In every other case the radiological appearances either remained the same or deteriorated and the sedimentation rate showed only minor variations. In no case did it decrease by more than 4 mm.

SUMMARY

1. Twenty-six cases treated with cadmium sulphide are reported.

2. Much larger doses were used than have previously been reported in the literature.

3. The possibility of toxic effects is considered.

4. The results were entirely negative and we cannot, therefore, confirm the optimistic reports of previous workers.

SUMARIO

1. Preséntanse 26 casos tratados con sulfuro de cadmio.

2. Utilizáronse dosis mucho mayores que las previamente comunicadas en la literatura.

3. Considéranse los posibles efectos tóxicos.

4. El resultado fué absolutamente negativo, sin que se confirmara en nada el optimismo de autores anteriores.

REFERENCES

(1) WALBRUM, L. E.: Ztschr. f. Immunitätsforsch., Bd. 47, Heft 3/14.
(2) LUND, N.: Ztschr. f. Tuberk., 1927, *48*.
(3) MAIGRE AND REYMIER: Rev. de méd., 1932, *49*.
(4) HEAF, F.: Brit. J. Tuberc., 1937, *31*, no. 2.
(5) CORNWALL, V. C.: Tubercle, 1938, *19*, 542.
(6) ROBERTS, B.: Brit. J. Tuberc., 1939, *33*, no. 2.

ADDENDUM

At the same time as the above study on the effect of cadmium on tuberculosis, we carried out similar work on a group of adult Bantu lepers of both sexes. In all, 38 lepers were studied. They were predominantly of the nodular type, but a few of the maculo-anaesthetic type were also treated. They all had a positive nasal smear and were ambulant cases.

Of the 38 patients, 18 received less than 20 cc. of cadmium sulphide, while the remaining 20 received amounts varying between 22 cc. and 52 cc. The treatment consisted of weekly injections of 2 cc. of 1 per cent cadmium sulphide in olive oil, and extended over a period of three to six months.

Results: There were no striking results. Of the group of 38, one patient was discharged six months after the cadmium therapy was stopped. This man had had a total of 48 cc.; one man died from heart failure about three months after he had had 22 cc. of cadmium. The remaining 36 showed no recognizable clinical improvement; nasal smears were all positive at the end of the treatment and the blood sedimentation rate showed no significant change.

INFECTION, SOCIAL ENVIRONMENT AND HEREDITY IN TUBERCULOSIS[1]

As Measured by Mortality Studies in Husbands and Wives, Brothers and Sisters

GEORG WOLFF AND ANTONIO CIOCCO

I. THE PROBLEM

Tuberculosis is an infectious disease; there is no doubt that the tubercle bacillus is the causative microbiological agent. Tuberculosis is, however, not to be compared with the acute infectious diseases in which the microbiological agents, bacilli, protozoa or viruses, dominate and determine the course and final outcome of the disease, mostly in a few days or weeks. Tuberculosis is a very chronic disease, the subsequent course of which, after the primary infection has taken place, is determined by the social environmental conditions under which the individual is compelled to live, as well as by his hereditary constitution. None of these three most important components—specific infection, social environment and hereditary factor—must be overrated as has been done very often, but they should be always differentiated in modern aetiological research since all three determine the outcome of the disease (Wolff (1)).

It is difficult to delimit the quantitative relationship of these three most important factors in more exact terms. Married couples, for instance, of whom one spouse has contracted tuberculosis may live for many years in close contact; brothers and sisters who, besides having a more definite constitutional relationship with each other, may also have lived together for years; yet tuberculosis of one member of the group need not be transferred to the other members of the group. This has been found by many investigators (see Weinberg (2), Münter (3)) and may be due to different constitutional types in interaction with the other aetiological components. On the other hand, identical twins behave more uniformly with regard to tuberculosis infection than binovular (non-identical) twins (Diehl and v. Verschuer (4), Uehlinger and Künsch (5)). This is to be expected, but it would involve a logical fallacy to see in such a behavior of tuberculosis the criterion of a predominantly inherited disease. For it is a commonplace that also in other infectious diseases, even the acute ones, or in injuries from external causes, individuals of the same hereditary make-up react on the average more uniformly than individuals of different or partly different genetic make-up.

II. NEW RESULTS ON MORTALITY IN HUSBANDS AND WIVES

In the new methodological study on the mortality in husbands and wives Ciocco (6), by applying the chi-square test to the stated causes of death in a large number of married couples (2,571) who died in Washington County, Maryland from 1898 to 1938, could demonstrate a distinct association between the spouses with respect to four causes of death: tuberculosis, influenza and pneumonia, can-

[1] From the Division of Public Health Methods, National Institute of Health, U. S. Public Health Service.

cer and heart diseases. In all four instances this association was significant from the statistical point of view; however, it appeared by far the most striking for tuberculosis. Chi-square for tuberculosis as cause of death in both husband and wife, when calculated from a fourfold tabulation, equals 23.87; the probability that such concurrence could arise by chance is exceedingly small ($P < 0.000,1$). Chi-square for influenza and pneumonia in the same sample amounts to 9.94, for heart diseases to 5.02, for cancer and other malignant tumors to 4.98 with the probabilities (P) being 0.0016, 0.0251, and 0.0257, respectively. Thus, since P is less than 0.05, which has the meaning that out of 100 trials less than 5 would show differences of the observed magnitude merely by chance, the deviations in the present instances between observation and expectation may be regarded as statistically significant if Fisher's (7) criterion is accepted. The finer details of the method applied and of the results obtained for the other causes of death may be found in the original paper.

When the observed numbers of the 2,571 husbands and wives were arranged in a contingency table according to the different stated causes of death and the numbers expected were calculated, assuming random matings in relation to cause of death, the following results were obtained: Observed number of husbands and wives both of whom have died of tuberculosis = 20, expected number (transferring the probability of dying from tuberculosis of the whole male or female population to the respective group under observation of the other sex) = 7.4; observed pairs of husbands and wives who died of influenza and pneumonia = 27, expected number = 15.5; observed number of both partners dying of cancer and other malignant tumors = 29, expected = 19.9; observed number of both marital partners with heart diseases as cause of death = 184, expected = 162.6. In contrast, for the other stated causes of death of both husband and wife, nephritis, cerebral haemorrhage and arteriosclerosis, the differences between observed and expected numbers are small and have no statistical significance.

Let us dwell still further upon the original 2,571 married couples of whom 117 men and 163 women died of tuberculosis. That is, among all deaths of the sample a percentage of 4.55 for the male and 6.34 for the female sex. These 280 persons who have died of tuberculosis comprise 20 couples = 40 marital partners both of whom had contracted the fatal disease, or 14.3 per cent, and 240 persons (97 men and 143 women) or 85.7 per cent, whose spouses died from other diseases than tuberculosis. It clearly demonstrates that even in tuberculosis the large majority of the persons subject to the greatest risk (husbands and wives of the tuberculous in the most advanced stages) did not die of tuberculosis. They probably contracted the disease but overcame the infection, or at least died from some other cause. On the other hand, if we now compute the frequency of tuberculosis deaths among the spouses of all those persons who died from other causes [(2,571 − 117) men + (2,571 − 163) women] we get a percentage of 4.9 (240 deaths from tuberculosis among 4,862 persons at risk). This is only one-third of the above tuberculosis frequency among spouses of those who have themselves died of tuberculosis.

If we divide the total material of death from tuberculosis and from other

causes as a whole according to sex, we obtain the following summary:

	per cent
Of 117 husbands who died from tuberculosis, 20 wives also died of the same cause	17.1
Of 2,454 husbands who died from other causes, 143 wives died from tuberculosis	5.8
Of 163 wives who died from tuberculosis, 20 husbands also died of the same cause	12.3
Of 2,408 wives who died from other causes, 97 husbands died from tuberculosis	4.0

Thus, for both sexes it can be said that when one of the spouses has died from tuberculosis the relative number of their husbands or wives dead from this cause is three times as high as that of the husbands or wives of those who have died from causes other than tuberculosis. The latter large group represents, so to speak, the control group from a general population of a similar age and civil state (married people) without having the same risk of living together with a tuberculous partner.

III. TUBERCULOSIS MORTALITY IN HUSBANDS AND WIVES AND THEIR BROTHERS AND SISTERS

In another methodological study, Ciocco (8) has supplemented the findings on husbands and wives by considering also the blood relatives of the spouses, namely, for an adequate comparison with the married couples, the sisters of the husbands and the brothers of the wives. All of them were also married or of marriage age in order to deal with homogeneous groups as far as possible with respect to age and marital state. By so doing, two broad familial groups could be contrasted: the husbands and wives who represent pairs not blood-related in the great majority of cases but living together under the same social conditions and in close personal contact for years and years; and the brothers and sisters of the respective spouses, the siblings constitute a group of blood-related persons of closely similar constitutional make-up who may also have lived together for quite a while under similar social environment and in more or less personal familial contact.

If A denotes the constitutional factor, B the social factor, C the infective (specific) factor, there are, then, two groups of association with the following designations:

Group I (husbands and wives): A $\neq$, B and C = [2]
Group II (brothers and sisters) [3] : A $\sim$, B and C $\sim$

In the first group of men and women, the main difference lies in the constitutional make-up (A) of both (marital) partners, social environment and risk of

[2] $\neq$ means unequal; = means equal; $\sim$ means similar.

[3] They are indeed not simple brothers and sisters as independent pairs, but rather the sisters and brothers of the husbands and wives, respectively, and therefore also blood-related to either of them. For shortness, the simple term "brothers and sisters" may be applied here and in the following pages under the assumption just mentioned.

infection (or other specific causation of disease) being practically the same; in the second group of men and women (brothers of the married sisters and sisters of the married brothers) all three factors are to a certain degree related and similar with each other but neither of them absolutely identical in the pairs concerned. Even the constitutional factor (A) is not identical in the blood-related pairs; for only monovular (identical) twins are assumed to have the same hereditary constitution. Brothers and sisters can never be identical twins but beyond question represent a much closer constitutional type of couples than husbands and wives. The social factor (B) and the specific factor (C) may be assumed to be similar for brothers and sisters if not equal, at least as long as they live together in the familial aggregate of the parental environment; however, after the separation from there and, hence, always after marriage, often a different social environment is acquired and the risk of infection may change, too. For this reason, the time factor (duration of common childhood; duration of marriage) as well as the dosage of infection resulting from a more or less intimate contact has to be considered. Thus we may be entitled to say that for brothers and sisters in our sample the social and infective risks are to be designated as similar in kind but not identical in quantity. Since marriage life lasts, on the average, about twice the length of life prior to marriage, a quantitative approach with regard to the weight of the factors could perhaps be attempted.

In the new study a total of 968 couples of husbands and wives were mentioned of whom an equal number of brothers and sisters could be found in the death records from 1898 to 1938 in Washington County (Maryland) Health Department. Thus the investigation comprises: 968 husbands and 968 brothers of their wives, and correspondingly 968 wives and 968 sisters of their husbands. One sib of each pair is also a spouse. According to the preceding lines, the characteristic differentiation between the couples is: non-blood relatives (husbands and their wives) and blood relatives (brothers and sisters of those).[4]

Among the 968 couples of married men and women and of brothers and sisters, respectively, the proportional frequency of the major causes of deaths are presented in table 1. The cause of death as recorded on the death certificate has been coded according to the International List (1929 revision); and when two or more causes were mentioned the rules given in the third edition of the Manual of Joint Causes of Death (1933) have been followed. The numbers of the groups of causes of death are added in the table.

Apart from the sex differences with respect to mortality from the stated causes of death, there are some more differences in the groups of the same sex. However, we will not put too much emphasis upon these smaller differences none of which is statistically significant, all the more since the proportional frequency of one cause of death (that is, the proportion among all deaths) is

[4] It may be mentioned that in the case of 220 spouses the death records of more than one sib of the opposite sex have been found. In order to compare pairs of sibs with married couples it has been necessary to select one sib only. This selection has been made by choosing the sib whose age at death was nearest to that of the spouse of the index case. (For more details see Ciocco (8).)

also dependent to some degree on the respective frequency of the other causes of death.

In discussing now in particular the meaning of tuberculosis mortality in the sample of 968 pairs of sibs related to as many pairs of spouses, reference regarding the methods applied was first to be made to the above mentioned paper (8). The data presented in table 2 furnish the results, determining (*a*) the

TABLE 1

Frequency of major causes of deaths in a sample of 968 married men and women, and 968 brothers and sisters of them, who died in Washington County, Maryland, 1898–1938

CAUSE OF DEATH	INTERNATIONAL LIST NUMBER	MEN		WOMEN	
		Number	Per cent	Number	Per cent
A. Husbands and wives					
Tuberculosis (all forms)	23–32	51	5.27	71	7.33
Influenza and pneumonia (all forms)	11; 107–109	59	6.10	83	8.57
Arteriosclerosis	97	62	6.40	40	4.13
Cancer and other malignant tumors	45–53	64	6.61	112	11.57
Nephritis	130–132	122	12.60	92	9.50
Cerebral haemorrhage and softening	82	159	16.43	125	12.91
Heart diseases	90–95	231	23.86	249	25.72
Other and ill-defined causes		220	22.73	196	20.25
Total		968	100.0	968	100.0
B. Brothers and sisters					
Tuberculosis (all forms)	Numbers as above	50	5.17	62	6.40
Influenza and pneumonia (all forms)		60	6.20	76	7.85
Arteriosclerosis		60	6.20	29	3.00
Cancer and other malignant tumors		70	7.23	120	12.40
Nephritis		137	14.15	116	11.98
Cerebral haemorrhage and softening		142	14.67	152	15.70
Heart diseases		237	24.48	230	23.76
Other and ill-defined causes		212	21.90	183	18.90
Total		968	100.0	968	100.0

percentage frequency with which both spouses and sibs have died from tuberculosis among spouses (index spouses) of whom one partner has died of tuberculosis, and (*b*) how this frequency compares with that observed for tuberculosis in all spouses and all sibs, respectively, of the sample. The term "index case" used in the table is to indicate the husband or wife of the original sample for whom the death record of an adult sib of the opposite sex, a brother of a wife

or a sister of a husband, has been uncovered in the files. Thus, all the index cases or index spouses must cover, of course, the whole sample of 968 pairs and represent, segregated by causes of death, the totals for which the percentages are calculated of those spouses and sibs who have died from the same cause of death as the index cases.

The other specified causes of death are added in the table for comparison; however, the further discussion will deal in the main here with tuberculosis and other respiratory infectious diseases. There are no significant differences in the proportional frequencies of causes of death between all sibs and all spouses, as can easily be seen from the percentages and their standard errors, except in the case of nephritis. What the reason may be for the higher nephritis frequency among sibs than among spouses is difficult to find out from this sample. But in general we may say that the proportions obtained for all sibs and all spouses represent a fairly good control measure to the proportions obtained among the sibs and spouses of the special index cases. Considering first—in accordance

TABLE 2

Percentages of sibs and of spouses who died from the same cause of death as the index cases

CAUSE OF DEATH OF INDEX CASES	NUMBER OF INDEX CASES	PERCENTAGE DEAD FROM STATED CAUSE AMONG			
		Sibs	Spouses	All sibs	All spouses
		Of index cases		In sample	
Tuberculosis	58	13.79	17.24	5.58 ± .74	6.61 ± .80
Influenza and pneumonia	67	11.94	16.42	7.13 ± .83	7.75 ± .86
Arteriosclerosis	51	0	7.84	3.93 ± .62	5.27 ± .72
Cancer	82	12.20	17.07	11.16 ±1.01	9.71 ± .95
Nephritis	117	12.82	11.11	14.05 ±1.12	10.02 ± .97
Cerebral haemorrhage	149	14.09	17.45	14.98 ±1.15	13.95 ±1.11
Heart diseases	239	23.01	31.38	23.55 ±1.36	24.90 ±1.39

with the former investigation—the spouses of the index cases, it is easily seen that among them the proportion of those who have died from the same cause as the index case is in all instances higher than the proportion of all spouses who died from the stated causes. However, only with respect to tuberculosis, influenza and pneumonia, cancer and heart diseases do the differences between the spouses both of whom have died from the same cause, and the general sample from which they are drawn, exceed the fluctuations of chance. This becomes manifest if we look at the respective differences and their standard errors.[5]

[5] Since the group of the index spouses is drawn from the general samples of spouses the condition of independence is not fulfilled for the respective proportions. Therefore, the standard error (ϵ) for the difference is computed by the formula

$$\epsilon \text{ diff.} = \sqrt{\frac{pq}{n_1 + n_2} \cdot \frac{n_2}{n_1}} = \sqrt{\frac{pq}{N} \cdot \frac{N - n}{n}} = \sigma \sqrt{\frac{N - n}{n}}$$

where N denotes the number of the entire sample, n the number of the sub-sample, $n_1 + n_2 = N$. See G. U. Yule and M. G. Kendall (9): An Introduction to the Theory of Statistics, 11th ed., 1937, p. 362.

They are:

	per cent
Tuberculosis	10.63 ±3.17
Influenza and pneumonia	8.67 ±3.15
Cancer	7.36 ±3.12
Heart diseases	6.48 ±2.43

Due to the smallness of the sample the computed errors of the index cases must be relatively high, but nevertheless the differences are in all probability statistically significant for these four causes of death, the most again for tuberculosis. This finding is in close agreement with the results reported above for the original sample and indicates that this smaller sample of 968 couples is representative of the total sample of 2,571 husbands and wives from which it has been selected for the present purpose of comparing both spouses and sibs of the same index cases. Reviewing now in table 2 the results of the sibs and comparing the frequency with which the sibs of the index cases and the sibs of the whole sample of 968 pairs have died from the same cause as the index cases it is obvious that only in the case of tuberculosis there is a larger difference. Among the 58 sibs of the index cases that died from tuberculosis, 13.79 ± 4.59 per cent also died from tuberculosis as compared to only 5.58 ± .74 per cent among all 968 sibs of the sample. Thus the difference and its standard error computed as before amounts to 8.21 ± 2.93 per cent and can be assumed to be statistically significant, as the small number of 58 index cases is considered to be a subtotal of the entire sample.

The above difference is not quite so significant as that between the corresponding spouses of index cases and all spouses of the same sample which amounted to 10.63 ± 3.17 per cent. But both differences clearly demonstrate that distinctly more spouses and sibs of persons who died from tuberculosis also died from this cause than would be expected on the basis of chance alone. It may further be mentioned that the ratios of the tuberculosis frequencies in both groups under observation are very closely similar. The relative frequency (17.24 per cent) among the spouses of those persons (index spouses) who have also died from tuberculosis is 2.61 times as high as that of all spouses (6.61 per cent); the relative frequency (13.79 per cent) among the corresponding sibs of those persons is 2.47 times that of all sibs (5.58 per cent).

It must be noticed that for all other stated causes of death, except tuberculosis, the sibs of the index cases died from the same cause with about the same frequency as the sibs of those who died from other causes. This can easily be taken from the percentage figures in table 2. Even the somewhat higher frequency with which the sibs of the index cases died from influenza and pneumonia than all sibs together is not statistically significant, the difference being 4.81 ± 3.04.

It is further noteworthy in this sample that more spouses of those who died from tuberculosis, influenza and pneumonia, cancer and heart diseases also died from these diseases than did the blood-related sibs of the same index cases. Thus for all four causes of death where a statistically significant association in the marital partners has been found, it is remarkable that more spouses than

sibs of the index cases died from the same cause. This may point to the cautious conclusion that, whatever the biological aetiology may be, on the average the long intimate contact in married life involves some more risk than the common constitutional and social components, as conditioned by blood relationship. To be sure, all these differences between the percentages of spouses and of sibs who died from the same cause as the index cases are not statistically significant (significance is only approached in heart diseases). The differences are in:

		per cent
Tuberculosis	17.24−13.79 =	3.45 ±6.72
Influenza and pneumonia	16.42−11.94 =	4.48 ±6.06
Cancer	17.07−12.20 =	4.87 ±5.51
Heart diseases	31.38−23.01 =	8.37 ±4.05

TABLE 3

Percentages of (a) sisters and (b) wives who died from the same cause of death as their respective brothers and husbands and percentages of (c) brothers and (d) husbands who died from the same cause of death as their respective sisters and wives

CAUSE OF DEATH OF THE MEN OR THE WOMEN	PERCENTAGE DEAD FROM THE STATED CAUSE AMONG					
	Sisters / Wives		All women in sample	Brothers / Husbands		All men in sample
	Of the men			Of the women		
	(a)	(b)		(c)	(d)	
Tuberculosis	16.00	19.61	6.87 ± .57	12.90	14.08	5.22 ± .51
Influenza and pneumonia	13.33	18.64	8.21 ± .62	10.53	13.25	6.15 ± .55
Arteriosclerosis	0	6.45	3.56 ± .42	0	10.00	6.30 ± .55
Cancer	14.29	21.88	11.98 ± .74	8.33	12.50	6.92 ± .58
Nephritis	10.95	10.66	10.74 ± .70	12.93	14.13	13.38 ± .77
Cerebral haemorrhage	14.79	16.35	14.31 ± .80	13.82	20.80	15.55 ± .82
Heart diseases	23.21	32.47	24.74 ± .98	23.91	30.12	24.17 ± .97

This of course must be expected due to the smallness of the samples, especially in the first three instances. These samples are independent from each other (spouses *or* sibs of the same index case) and thus exhibit a relatively large standard error. However, all the differences point to the same direction, thus emphasizing the higher frequency of these causes of death in spouses as compared to sibs and may have some real meaning for the further discussion.

Anyhow, the most important fact in the results of this study is that *only with reference to tuberculosis* is there a distinct association among siblings as well as among marital partners, almost equally significant in the two groups, the relative frequency being nearly three times that of all sibs and spouses.

Before we discuss this special item in greater detail, the respective findings may be enlarged by segregating the sexes and comparing separately brothers and sisters with husbands and wives. The results obtained are presented in table 3.

From this table it is seen again that the relative frequency of tuberculosis as a cause of death among the wives of men who died also of tuberculosis is 2.9

times as high as that for all women; the relative frequency among sisters is 2.3 times that for all women. The deviations from the latter average are in both instances statistically significant. The same holds true for the males. The relative frequency of tuberculosis among the husbands of women who died of tuberculosis is 2.7 times, among brothers is 2.5 times that for all men in the sample.

With reference to the other stated causes of death there is, as may be taken from the data of the table, a distinct association also in influenza and pneumonia, cancer and heart diseases between husbands and wives, but for none of the specific causes, except tuberculosis, is there a significant tendency between brothers and sisters to die from the same cause.

All the findings relative to husbands and wives reveal in principle the same results as obtained in the larger sample of 2,571 couples of the original investigation (6). But the addition of brothers and sisters in the subsample of 968 pairs makes it evident that, with regard to the stated single causes of death, only relative to tuberculosis is there a statistically significant concurrence between brothers and sisters as well as between husbands and wives to die from the same cause. The findings obtained so far in tuberculosis could be explained on the basis of the infective factor alone; the manifestations in brother-sister pairs, however, could also be due, at least partly, to some common genetic factor. For it must be recalled that in these sibs a long interval, as a rule, lies between the period of early infection and the age at death from the infection. This time lag can hardly be explained by the specific factor alone. Either unfavorable social conditions in adult life (occupation, etc.) or some inborn constitutional susceptibility after sexual maturation could cause the late outbreak of the disease.

IV. MORTALITY IN SIBS AND SPOUSES FROM DISEASES OF THE RESPIRATORY SYSTEM

It is certainly indisputable that inherited factors of a particular anatomical and physiological body constitution play an important part in the pathology of most diseases. This is accepted by most students of human pathology for many years, clinicians as well as geneticists (Martius (10), Kraus (11), Bauer (12), Pearl (13), Long (14), etc., to mention only a few). But a precise differentiation of what are the special characteristics of hereditary qualities predisposing to the development of tuberculosis has not yet, unfortunately, been discovered in animal experiments or by recent investigations of pedigrees in tuberculous families or twin research any more than by the early assumptions of a typical *habitus phthisicus* or *asthenicus* (Beneke (15), Stiller (16)).

However, several investigators in studying the possible hereditary factors as determined through a suitable disposition of the infected individual, have already simplified the problem by assuming not so much a specific susceptibility to tuberculosis but rather an organ predisposition for infectious diseases of the lungs as a whole, thus including pneumonia, influenza, bronchitis, etc. Tuberculosis is certainly an exogenous infection caused primarily by the specific germ

as any other infectious disease; it is hardly an inherited disease in the sense that a special "tuberculosis gene" is the main basis of the disease. Yet it seems to be reasonable to assume some kind of a common constitutional susceptibility of the lungs to become infected and therefore to consider tuberculosis as a cause of death not singly in terms of a clinical or aetiological entity but combined with other infections of the same organ. Münter (3), in an exhaustive study on pedigrees of 33 families in a certain rural district in Baden, Germany, for instance, attempted on genetic lines to reach the conclusion of a recessive inheritance for such a common constitutional factor in predisposed individuals. He called particular attention to the well known clinical fact that often members of the same family, even brothers and sisters, react differently to tuberculosis and related respiratory diseases. Those members of the family remaining healthy he assumed to be heterozygotic, not showing the recessive character; those suffering and dying from open tuberculosis are supposed to be homozygotic with regard to the factor or, in practice, to have it received from both the parents.

Whatever may be the final conclusions regarding this daring hypothesis which can be examined only by further extensive pedigree studies in tuberculous fami-

TABLE 4

Percentages of sibs and spouses who died from respiratory diseases, as compared to those in which the index case died from other than respiratory diseases

CAUSE OF DEATH OF INDEX CASE	NUMBER OF INDEX CASES	PERCENTAGE OF DEATHS FROM RESPIRATORY DISEASES AMONG	
		Sibs	Spouses
Respiratory diseases	125	21.6 ± 3.7	28.0 ± 4.0
Other than respiratory diseases	843	11.2 ± 1.1	12.3 ± 1.1

lies, it seemed to be worth while to combine also in the present investigation the mortality from causes connected primarily with the fatal breakdown of the respiratory system. The frequency with which sibs and spouses of persons who died from tuberculosis of the lungs plus influenza and pneumonia also died from these diseases of the respiratory system is presented in table 4.

The data presented in the summary clearly demonstrate that, both among the sibs and the spouses of persons who died from respiratory diseases, the proportion that died from the same causes is distinctly higher than that observed among the other sibs and the other spouses. The association is in both groups statistically significant, the differences and their standard errors being:

For sibs ..... 10.4 ±3.86
For spouses ..... 15.7 ±4.17

The concurrent tendency is slightly more marked in spouses. This finding with respect to the spouses is, of course, to be expected since it was shown above that spouses of persons who died either from tuberculosis or from influenza and pneumonia demonstrate a significant tendency to die from the same causes. This held also true for sibs of persons who died from tuberculosis; but among the

sibs of those who died from influenza and pneumonia, although the proportion of death from these diseases was larger than among other sibs, the magnitude of the difference could still be due to chance. Yet, by combining tuberculosis with influenza and pneumonia, it results that for the respiratory group of diseases as a whole both the sibs and the spouses of persons who have died from such causes die from the same group of diseases significantly more often than sibs and spouses of persons who died from other causes. Considering that the sibs (in our sample they are of different sexes) were separated relatively early and particularly by marriage, but died mostly in adult and old age from diseases of the respiratory system, the conclusion suggests itself that there is a constitutional factor involved. The conclusion would not be cogent for tuberculosis alone on account of the chronicity of this infectious disease. It could be acquired in childhood but, for reasons not yet fully explored, develop much later over a period of latency into the fatal stage of the disease; the concomitant social factors probably playing another important part in this development. But such an explanation is impossible for acute infectious diseases like influenza and pneumonia. Thus the conclusion seems justified that there is also a constitutional factor regarding the susceptibility of the respiratory system as a whole; a conclusion very similar to that reached by Münter's entirely different methods of investigation.

V. DISCUSSION

Because of the complexity of the problem which involves the measurement of environment and heredity as causative factors, the results obtained for tuberculosis only and other infectious diseases of the respiratory system will be discussed in the light of modern aetiological research. These results are obtained by a new statistical approach to the study of familial aggregates, husbands and wives on the one side, their brothers and sisters on the other. The marital pairs are nonrelated individuals living in close intimacy and may represent the influence of environment in particular to which, of course, infection becomes a subfactor or the so-called specific factor. In the pairs of brothers and sisters, one of whom is also a spouse (index spouse) of the other group, the constitutional or hereditary factor comes in. It may aggravate a disease, the infectious origin of which has been set in the common childhood and the parental surroundings.

The principal results of the study are briefly summarized:

(*1*) In the sample of 968 husbands and wives the association relative to death from tuberculosis and from influenza and pneumonia is very distinct and statistically significant. The percentage of deaths from tuberculosis among spouses of tuberculous index spouses is 17.2, or 2.6 times as high as among all spouses of the sample with a relative frequency of 6.6 per cent deaths from tuberculosis. The corresponding percentages for influenza and pneumonia are 16.4 among spouses of index cases who have died from the same cause and 7.8 among all spouses, that is, a ratio of 2.1 to 1. The differences are statistically significant in both instances. This finding is in good agreement with the results reported upon in a larger original sample of husbands and wives.

(*2*) Among the dead brothers and sisters of spouses who have died from tuberculosis, this cause of death is almost as frequent as among the spouses of these persons (index cases) and by far more frequent than among the sibs of those persons who died from other causes. The corresponding percentages in sibs are 13.8 and 5.6, or a ratio of 2.5 which is almost as high as in spouses. The difference is statistically significant as proved by the standard error of the difference in the entire sample and the subsample. This is not quite so for the deaths from influenza and pneumonia among sibs, although the proportion of deaths from these diseases among the sibs of persons (index cases) who died from the same cause is higher than among all sibs. The corresponding percentages are 11.9 and 7.1; the difference could be due to chance in the strict sense of the statistical theory.

(*3*) Finally, when influenza and pneumonia are grouped together with tuberculosis and thus combined in a major group of infectious diseases of the respiratory system, then it is evident from the results in this sample that, among sibs as well as among spouses of persons who died from such diseases, there is a statistically significant superiority in the relative frequency of these causes over sibs and spouses of persons who died from other causes. The corresponding percentages are in sibs 21.6 and 11.2, in spouses 28.0 and 12.3, which is a ratio of 1.9 and 2.3, respectively. The association of deaths from respiratory diseases is in both instances statistically significant as proved by the standard errors of the difference of both independent subsamples.

What is the social, aetiological and clinical meaning of these results considering only the statistically significant concurrence in the marital couples and the brother-sister pairs? A relative frequency of tuberculosis mortality of more than 17 per cent in both marital partners and of almost 14 per cent in both siblings is certainly a high incidence of fatal disease, especially when compared with the occurrence in the sample as a whole, 6.6 in all spouses and 5.6 in all sibs. It clearly demonstrates the great importance of the intimate contact with respect to tuberculosis in married people who are in general not genetically related to each other. But there is also an incidence almost as high among blood-related pairs when one of the pair has died of tuberculosis. The difference in the relative frequency of tuberculosis deaths between these spouses and sibs is not significant. Thus the pure effect of the chronic infection in marital partners is at least as high or even somewhat superior to the combined forces of a common genetic constitution and a common childhood environment in the siblings. Consequently, it could be concluded that the infective agent or the specific factor is of greater weight than the other factors involved in the development of tuberculosis as a cause of death. However, there is one restriction on this simple and seemingly obvious conclusion to be made, even in the case of the relatively high frequency of mortality from tuberculosis in spouses, one of whom has already died of the disease. Considering that these husbands and wives have lived together for many years in the closest contact thinkable and in the same social environment, it is indeed surprising that no more than 17 per cent of them have died from the same infection; as a matter of fact, 83 per cent have

not, or by far the larger majority of spouses in whom the same source of infection was present for years and, of course, the same social environment. They all have probably acquired the infection in the intimate contact but they did not die of it. Similar observations have been repeatedly reported in tuberculosis literature.

Already Pearson (22), in an early investigation of this kind, arrived at similar conclusions. His results of association between husbands and wives, parents and children with regard to tuberculosis show that the father is twice as dangerous to the child as the husband to the wife; further that the mother is only slightly more dangerous than the father at very early ages of the children. Consequently, he asks: "If the main factor be infection why should the father and mother be equally influential with their children, and why should the father be twice as influential as the husband?" And thus he concludes, beyond doubt somewhat overstating his point: "The hereditary constitutional factor is immensely more important than the infection-factor" (l.c. pages 19 and 20).

In this connection, some remarkable results in recent experimental work (Lurie (17)) may be quoted concerning resistance or susceptibility in animal tuberculosis. By inbreeding brothers and sisters or parents and offsprings over several generations of six rabbit lines, each of which was infected with bovine type of tubercle bacilli, Lurie finally obtained three different groups of animals with respect to tuberculosis resistance. One line was characterized by slow progression of the disease, long life after infection, that is, displaying high resistance to tuberculosis. In contrast, two other lines, throughout the experiment, exhibited tuberculosis characterized by progressive and rapid course, that is, displaying uniformly high susceptibility. In the remaining families the tuberculosis was intermediate. (For the finer pathological anatomical differences, see the original.)

Long (18) in an exhaustive review on the whole matter of constitution in tuberculosis summarizes these findings as follows:

"Thus there seemed no doubt that a true difference between strains existed, and since this bred true in generation after generation, it appeared to be on a hereditary basis. Sex, age and color of coat were not associated with differences in resistance. In other words, the transmissible characters affecting resistance were not sex linked, and resistance could not be predicted from the appearance of the animals."

These latest animal results resemble indeed in many respects observations in human families and will also have a special bearing upon our present findings in man. In this respect we may also quote the Swedish clinician Wallgreen (19) who among other students of human tuberculosis has strongly emphasized the hereditary side of tuberculosis. In a thoughtful paper describing the possible development of the disease from childhood infection to adult type of pulmonary tuberculosis he reviews his experience:

"Pulmonary tuberculosis is usually not the immediate result of introduction of tubercle bacilli either from the outside or the inside into the allergic lung, but is rather the effect of activity by tubercle bacilli, which in most cases of pul-

monary tuberculosis have long remained in the same place, but have not been able to start a progressive process on account of resistance on the part of the organism and especially the lungs." Thus he concludes that "variations in resistance in the infected organism and especially in the infected tissue make it possible that some individuals contract pulmonary tuberculosis and others do not."

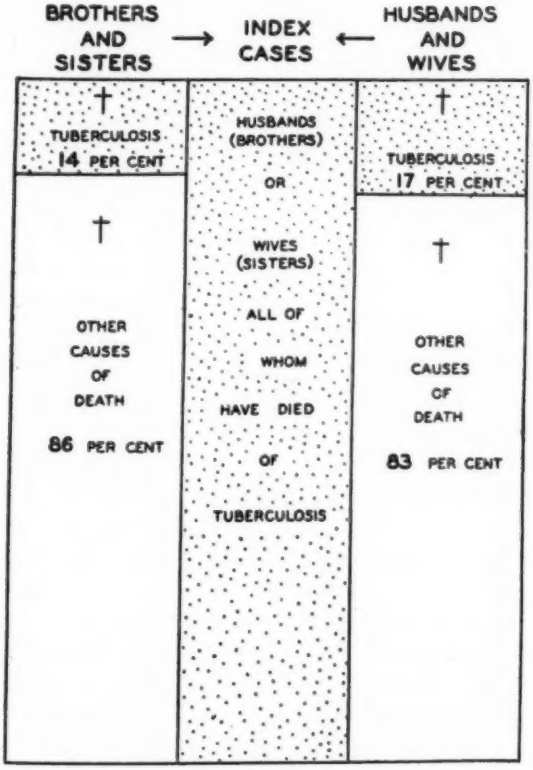
Wallgreen's opinion may at first appear somewhat extreme, but he probably expresses the opinion of many writers who have recently reëxamined the concept of tuberculosis pathogenesis when he summarizes his views in the sentence: "Without infection no tuberculosis and without disposition no consumption." True, also, in the present study the concentration of deaths from tuberculosis among marital partners is relatively high when compared with nonmarital groups of the same age and sex composition or with married couples of whom one spouse has died of other causes of death. But students of tuberculosis epidemiology have often been surprised to find that the association of death from such an outspoken chronic infection is not higher in husbands and wives. In the present sample five times as many spouses did not die from tuberculosis as did after the other spouse had become a victim of the fatal disease.

What can be assumed to be the possible explanation of these negative findings in spouses in both of whom the specific factor (chance of infection) and the social factor (common environment) may be taken as approximately 100 per cent equal?

There is only one factor left supposed to be different in husbands and wives with respect to tuberculosis; that is the constitutional make-up of the spouses. If this is true then it seems to be logical that the third major factor, the inborn constitution, which of course plays a part in every disease (Martius), has prevented the tuberculous infection from becoming active disease or the cause of death in a majority of equally exposed marital partners. Thus these findings in husbands and wives shed also some light upon the general importance of the constitutional factor in tuberculosis. However, a more precise differentiation of what are the special hereditary qualities of such a constitution, the one of which leads to frank tuberculosis and the other does not, cannot be revealed from death certificates alone. This would be an important clinical task for the future in investigating living husbands and wives exposed to tuberculosis during lifetime by special anthropometric and constitutional methods to be supplemented if possible by autoptic findings.

With this conclusion regarding the potential constitutional factor in the presence or absence of tuberculosis in married couples, we turn to the findings in brother-sister pairs. That there is a constitutional factor involved is beyond question. However, the relative importance of a common genetic constitution is not so easily to be delimited from the common source of infection which took place probably in the childhood of the siblings. If the high frequency of 14 per cent deaths from tuberculosis among brothers and sisters of tuberculous index cases—reported in the present investigation as compared to only 5.6 per cent among all sibs—is explainable on the basis of a common childhood in-

fection alone and a possible later reinfection, endogenous or exogenous, in adult life, then the time interval between first infection and age at death, mostly in later life, is noteworthy and offers some more difficulties for a clear-cut conclusion from the point of view of contagion. For it must be kept in mind that these brothers and sisters, after childhood, as a rule, did not live in the same "tuberculous milieu." But when they came to die in later life they died of tuberculosis, or more exactly speaking, 14 per cent of them did. Thus the constitutional



RELATIVE FREQUENCY OF MORTALITY FROM TUBERCULOSIS AND FROM OTHER CAUSES OF DEATH IN SIBS AND SPOUSES OF PERSONS (INDEX CASES) WHO HAVE DIED OF TUBERCULOSIS

GRAPH 1

factor probably enters the picture. And it seems still more conclusive than in husbands and wives that only those brothers and sisters died of tuberculosis who were born with a constitution favorable to the infection. It means again that the large majority of them did not die of tuberculosis, although they all had the same kind of blood-relationship to a tuberculous index case who had died from the disease. The relations may be illustrated in graph 1.

At this stage of the discussion it is to be recalled that blood-relationship,

although constituting some common genetic factors, does not implicitly mean a constitution favorable or a positive predisposition to tuberculosis; it can also mean the contrary or a constitution affording protection against the disease. Yet in the present sample the brothers or sisters are sibs of spouses who have themselves definitely shown tuberculosis susceptibility; therefore they exhibit the same susceptibility which led to death from tuberculosis in a high and statistically significant proportion, when compared with sibs of persons who did not die from tuberculosis. On the other hand, such a positive disposition to tuberculosis was not present in the majority of the sibs or, at least, not manifest. In this respect we may refer to Münter's above-mentioned hypothesis and have to confirm, anyway, what was the starting point of his investigations of pedigrees, namely, the different reactions of siblings in familial contact with tuberculosis.

On principle, similar conclusions can be derived from investigations on the behavior of tuberculosis in identical and non-identical twins. In this connection, the results of Diehl and v. Verschuer (4) may be quoted. They studied 127 pairs of twins in which one, both, or neither of the twins suffered from tubercu-

TABLE 5

*Behavior of monovular and binovular twins in respect of tuberculosis**

NUMBER AND KIND OF TWINS	BEHAVIOR IN RESPECT OF TUBERCULOSIS	
	Concordant	Discordant
37 identical pairs (monovular).....	26 = 70% ±7.5	11 = 30% ±7.5
69 fraternal pairs (binovular).....	17 = 25% ±5.2	52 = 75% ±5.2

* After the original results of Diehl and v. Verschuer.

losis and have shown a more or less clinically concordant or discordant behavior in respect to tuberculosis. The authors excluded 21 pairs in which no distinct evidence of tuberculosis was obtainable. With the remaining 106 pairs, 37 of which were identical (monovular) and 69 non-identical or fraternal (binovular) twins, the results shown in table 5 were reached.

The difference between the two groups with its standard error of 45 ± 9.1 per cent certainly is statistically significant.

In a later investigation (4b) the authors extended their studies to a total of 205 pairs (80 identical and 125 fraternal twins). The results obtained resembled very much the former ones; the identical twins demonstrated concordance of tuberculosis in 65 per cent, the non-identical ones in only 25 per cent, which is the same ratio as in the smaller sample. Similar results, on principle, were also obtained by Uehlinger and Künsch (5) with 46 pairs (12 identical and 34 fraternal twins) in Switzerland. Concordance, however, in this smaller sample with regard to tuberculosis was still less frequent among the 34 non-identical pairs; only 2 of them behaved concordantly, or scarcely 6 per cent, while among the 12 identical twins 7 demonstrated concordance of tuberculosis.

It is not surprising that monovular twins behave in regard to incidence and development of tuberculosis more uniformly than fraternal (binovular) pairs, by the mere fact that they represent genetically identical individuals. This, of course, does not mean that tuberculosis *per se* is an inherited disease, but it does mean that the constitutional make-up of an individual plays an important part in the course and final outcome of the disease as probably in many diseases. But what is still more important in these twin investigations—and that in good agreement with our findings—is the other fact that in the fraternal pairs, the genetic relationship of whom is the same as in normal siblings, concordance of tuberculosis was observed only in 25 per cent (in the small sample of Uehlinger and Künsch even in only 6 per cent). Thus the large majority of these fraternal pairs behaved differently in respect to tuberculosis although they had the same chance of infection.

From these observations the conclusion is probably justified that even in pairs as closely related as non-identical twins a constitutional factor determines to some extent the clinical outcome of tuberculosis. The criterion in the present investigation was death from tuberculosis as given by the diagnosis on the death certificate, the same was the case in Münter's pedigree studies over many decades back; in Diehl and v. Verschuer's examinations the criterion was the diagnosis of similarity in the behavior of living twin-couples as to concordance or discordance of tuberculosis which involves probably a good deal of difficulties on the part of the clinical judgment. Thus it could be explained why the association of deaths from tuberculosis in both siblings of brother-sister pairs amount to a still lower proportion in the present investigation (14 per cent) than the clinical concordance in fraternal twins after the results of Diehl and v. Verschuer (25 per cent). However, in both samples the large majority of those exposed to tuberculosis in familial contact did not develop the clinical disease. This could be due to a different social environment after childhood; it can be also attributed to a different constitutional make-up of the siblings. Such a different susceptibility to tuberculosis is still more convincing in the findings of husbands and wives exposed to tuberculosis for whom social factor and infective factor can be taken as equal in both spouses.

Bearing on the view that the constitutional element in the mortality from tuberculosis as a respiratory disease plays a rôle, are the findings relative to other infectious diseases of the lungs, that is, in the present investigation relative to the mortality from influenza and pneumonia. Such an association was not large enough to be statistically significant, although the proportion that died from these causes among the sibs of persons who also died from influenza and pneumonia is higher than among the sibs of persons who died from other causes. But when the deaths from influenza and pneumonia and from tuberculosis were grouped together, then there is a statistically significant association among spouses as well as among sibs for the major group of respiratory diseases.

The findings for influenza and pneumonia alone are interesting in particular with respect to a possible constitutional factor. First it might seem that an explanation of this association is easy on account of the infectious character of

the cause of death and analogous to tuberculosis. But keeping in mind that influenza and pneumonia are acute infectious diseases and recalling, on the other hand, from the introductory remarks that the deaths of husbands and wives as well as of brothers and sisters from this cause were not simultaneous, the association between spouses living together or sibs living apart cannot well be explained by the repeated transmission of the pathogenic agents as in tuberculosis. The transmission could be only indirect, due to the interval between the deaths of the two partners; either it is to be assumed that one partner has become a carrier or that the infective agent is ubiquitous and has acquired a particular virulence under circumstances not well known. These "explanations" are not very satisfactory; but anyhow, the positive findings as to influenza and pneumonia, especially in spouses one of whom has already died of the same cause, point to the possible influence of a constitutional or somatic factor, whereas in tuberculosis as an outspoken chronic infectious disease it is more the negative findings in a large majority of the exposed spouses and sibs which seem to indicate a constitutional protection against the outbreak of the disease. There is no doubt that all the spouses and probably all the sibs in the close familial contact with tuberculosis have been abundantly infected.

In addition, by combining the deaths from tuberculosis and from influenza and pneumonia, a statistically significant association relative to these respiratory diseases becomes evident for spouses as well as for sibs. This seems to indicate that the influence of a constitutional factor manifests itself in general with reference to the kind of respiratory system rather than to the specific action of a parasite such as the tubercle bacillus, the influenza virus or the pneumococcus. It may be recalled that Münter in his pedigree investigations started from a similar point of view assuming an organ predisposition rather than a specific gene for the single infectious diseases, whereas Diehl and v. Verschuer in their studies reached the view that a direct "tuberculosis gene" is the basis of a tuberculous predisposition. Thus the present findings in husbands and wives and in brothers-sisters pairs confirm to a certain extent the earlier view of a constitutional susceptibility more often expressed by students of constitution and disease prior to the extreme bacteriological era. They also fit into recently obtained results in animal experiments (Lurie), in which the conclusion was reached that genetic constitution is responsible for variations in tuberculosis resistance of different rabbit families but that it operates through a combination of still unknown factors.

If in this investigation the importance of a constitutional factor in tuberculosis and also other infectious diseases of the lungs is emphasized, the conclusions do not contradict the well established fact that in all infectious diseases the epidemic agent is a *conditio sine qua non*. Nor does the establishment of a constitutional factor interfere with the other well known fact, stated by numerous investigators and from different parts of the world, that social conditions prove highly important for the final issue of the actual disease. There is a definite differential in tuberculosis mortality between lower economic and well-to-do classes (1). However, if it is true that a constitutional factor also comes in as a third com-

ponent of tuberculosis pathogenesis, then many features in recent tuberculosis epidemiology are to be better explained. If there is a certain constitutional make-up predisposed to infections of the lungs as is most convincingly indicated by the positive association relative to influenza and pneumonia over long periods of time, the association for tuberculosis could be explained by the chronic infection alone; if, on the other hand, there are also kinds of constitution affording protection against the infection as made probable by the large amount of negative findings in sibs and spouses who lived in close familial contact with tuberculosis, then the most striking feature in modern tuberculosis epidemiology, the steady and almost uninterrupted decline of tuberculosis mortality since about the turn of the century, could be due, at least partly, to a steady constitutional selection.

It is a matter of fact that the sources of tuberculosis infection have greatly diminished during the last decades. This was already assumed by former investigations (see Frost (20)) and could be proved in a recent investigation on the present frequency of tuberculosis lesions in autopsies (Landé and Wolff (21)). If for a series of successive decades deaths from tuberculosis have affected especially those persons with a constitution susceptible to tuberculosis, the surviving population will be more fit to obviate the danger of new infection. Thus the old theory of natural selection by mortality from tuberculosis long ago brought forward by Karl Pearson (22) to explain the decline of tuberculosis mortality may have some real meaning. For practical purposes, however, it would be more important on the basis of new constitutional investigations to explore further what is the kind of constitution that affords protection against infectious respiratory diseases or, on the other hand, contains susceptibility toward such diseases.

However, the natural selection by the early death of the tuberculous probably does not explain the whole story of the epidemic course. The reproductive powers of the affected in a majority of cases continue until death from tuberculosis and mostly secure a maintenance of their stock. It must, in addition, be recalled that the decline of tuberculosis was interrupted during World War No. 1 almost in all European countries, somewhat even in the United States and Japan (23). The sudden rise speaks of the importance of other factors, probably social conditions and particularly national nutrition in years of scarcity as long as the infective agent, or the source of infection, is still present in a large part of the population. Thus, without exaggerating the meaning of a hereditary factor in tuberculosis aetiology and epidemiology, it may suffice to underline that there is a constitutional factor involved in the tuberculosis problem. It will be difficult to evaluate this factor quantitatively against the other ones, yet its significance can be newly demonstrated in man by the present findings in husbands and wives and their brothers and sisters. Certainly we cannot change the constitutional make-up of an individual. But it might be worth keeping in mind that there is an inborn constitution determining at least part of the outcome of the disease, which is often fully denied by extremists, the pure contagionists or the pure enthusiasts of social environment. All three groups of aetiological factors play their part, and it may be worth mentioning that a con-

stitutional component, by the way of selection, could even have something to do with the present downward trend in tuberculosis mortality in general or, for instance, with the parallel downward trend in the colored and the white race observed for many years in the U.S.A. in spite of the very different level of the mortality rate in both populations.

SUMMARY

1. In a sample of 968 husbands and wives and 968 brothers and sisters, one of whom is also a spouse of the former group (index spouse), the association of tuberculosis and of influenza and pneumonia as causes of death was examined. The material was collected in Washington County, Maryland between 1898 and 1938 and selected from a larger sample of 2,571 married couples.

2. Among husbands and wives there is a distinct and statistically significant association relative to death from tuberculosis and from influenza and pneumonia. When one spouse (index spouse) has died from tuberculosis, 17.2 per cent of the other spouses also died of the same cause, as compared to only 6.6 per cent deaths from tuberculosis among all 968 spouses of the sample. The corresponding percentages for deaths from influenza and pneumonia are 16.4 and 7.8. When the sexes are separately compared with all men and women in the sample, the findings are similar.

3. All the findings relative to husbands and wives reveal in principle similar results as obtained in the larger original sample. The addition of brothers and sisters in the subsample of 968 pairs makes it evident that also among the dead sibs of spouses who have died from tuberculosis, for this cause of death there occurs again a statistically significant association. Among these sibs, tuberculosis as cause of death is almost as frequent as among spouses, and again much more frequent than among all sibs of the sample, the corresponding percentages being 13.8 and 5.6. Yet the difference is not significant for deaths from influenza and pneumonia alone among sibs of persons who died from the same cause and among all sibs.

4. When the deaths from tuberculosis and from influenza and pneumonia are combined in a major group of infectious diseases of the respiratory system, then among sibs as well as among spouses there is evidence of a significant association of these combined causes of death. The corresponding percentages are in sibs 21.6 and 11.2; in spouses 28.0 and 12.3.

5. The negative side of the present findings must not be overlooked; 83 per cent of the spouses and 86 per cent of the sibs exposed to the same risk of tuberculosis for many years did not die of tuberculosis, although the other partner has died of it. Therefore, in addition to specific infection and social environment, the third major factor in the development of disease, the inborn constitution, has to be considered. The results in brother-sister pairs are comparable in this respect with those obtained in fraternal twins.

6. The significance of a constitutional element has been made probable also by the findings relative to other infectious diseases of the lungs, especially influenza and pneumonia. The distinct association for husbands and wives makes such an assumption almost cogent when keeping in mind that deaths from

these acute diseases did not occur simultaneously in the pairings. Thus the conclusion has been reached that the constitutional factor manifests itself rather with reference to the respiratory system as a whole than to the action of one of the specific parasites.

SUMARIO

1. En un grupo de 968 esposos y esposas, y 968 hermanos y hermanas (esposos del grupo anterior) (índice conyugal), se estudió la asociación de tuberculosis, influenza y neumonía. El material fué obtenido en el Condado Wáshington, del Estado de Máryland, de 1898 a 1938, y escogido de un grupo mayor de muestra de 2,571 matrimonios.

2. Entre esposos y esposas existe una asociación manifiesta y estadísticamente significativa con respecto a la mortalidad de tuberculosis y de influenza y neumonía. Cuando uno de dos esposos (índice conyugal) había muerto tuberculoso, 17.2 por ciento de los cónyuges también murieron de la misma causa, comparado con sólo 6.6 por ciento entre todos los esposos del grupo. Los porcentajes correspondientes de mortalidad por influenza y neumonía fueron 16.4 y 7.8. Cuando se comparan por separado los sexos con todos los hombres y mujeres del grupo, los hallazgos son semejantes.

3. Todos los hallazgos relativos a las esposas y esposos revelan en principio resultados semejantes a los obtenidos en la primera muestra mayor. La adición de hermanos y hermanas en una submuestra de 968 parejas pone de manifiesto que, entre los hermanos fallecidos de los esposos que han muerto de tuberculosis obsérvase también una asociación estadísticamente significativa para esta causa de muerte. Entre esos hermanos, la tuberculosis como causa de muerte es casi tan frecuente como entre los esposos, y además, mucho más frecuente que entre todos los hermanos de la muestra, siendo los porcentajes respectivos 13.8 y 5.6. Sin embargo, no existe diferencia importante en lo relativo a las muertes de influenza y neumonía solas entre los hermanos que murieron de la misma causa y entre todos los hermanos.

4. Cuando se combinan las muertes de tuberculosis y de influenza y neumonía en un grupo mayor de enfermedades infecciosas del aparato respiratorio, tanto entre los hermanos como entre los esposos obsérvanse señales de una asociación significativa de estas causas combinadas de muerte. Los porcentajes correspondientes son: entre los hermanos, 21.6 y 11.2; entre los esposos, 28.0 y 12.3.

5. No hay que pasar por alto el aspecto negativo de los hallazgos actuales; 83 por ciento de los esposos y 86 por ciento de los hermanos expuestos al mismo peligro de tuberculosis por muchos años no murieron de tuberculosis, aunque sus compañeros murieron de ella. Por consiguiente, además de la infección específica y el ambiente social, hay que tomar en cuenta el tercer gran factor en la producción de la enfermedad: la constitución ingénita. Los resultados en las parejas de hermano-hermana son comparables en este sentido a los obtenidos en los gemelos fraternales.

6. La importancia de un elemento constitucional resulta también más probable a la luz de los hallazgos relativos a otras enfermedades infecciosas de los pulmones, y en particular influenza y neumonía. La asociación bien definida para esposas

y esposos dota de más verosimilitud a esta suposición si se tiene presente que las muertes debidas a estas afecciones agudas no tuvieron lugar simultáneamente en las parejas. Se saca, pues, la conclusión de que el factor orgánico se manifiesta más bien con referencia al aparato respiratorio en conjunto que a la acción de uno de los parásitos específicos.

BIBLIOGRAPHY

(1) Wolff, G.: Tuberculosis and civilization, Human Biol., 1938, *10*, 106–123 and 251–284.

(2) Weinberg, W.: Lungenschwindsucht beider Ehegatten. Ein Beitrag zur Lehre von der Tuberkulose in der Ehe., Beitr. z. Klin. d. Tuberk., 1906, *5*, 365.
Weinberg, W.: Die Kinder der Tuberkulösen, Leipzig, 1913.

(3) Münter, H.: Lungentuberkulose und Erblichkeit, Beitr. z. Klin. d. Tuberk., 1931, *76*, 257.

(4a) Diehl, K., and v. Verschuer, O.: Zwillingstuberkulose, Zwillingsforschung und erbliche Tuberkulosedisposition, Jena, 1933.

(4b) Diehl, K., and v. Verschuer, O.: Der Erbeinfluss bei der Tuberkulose (Zwillingstuberkulose II), Jena, 1936.

(5) Uehlinger, E., and Künsch, M.: Über Zwillingstuberkulose, Untersuchungen an 46 Paaren, Beitr. z. Klin. d. Tuberk., 1938, *92*, 275.

(6) Ciocco, A.: On the mortality in husbands and wives, Human Biol., 1940, *12*, 508.

(7) Fisher, R. A.: Statistical methods for research workers, (last edition), Edinburgh and London, 1938.

(8) Ciocco, A.: On the mortality in brother-sister and husband-wife pairings, Human Biol., 1941, *13*, 289.

(9) Yule, G. U., and Kendall, M. G.: An introduction to the theory of statistics, 11th ed., London, 1937.

(10) Martius, F.: Konstitution und Vererbung in ihren Beziehungen zur Pathologie, Berlin, 1914.

(11) Kraus, F.: Die Ermüdung als Mass der Konstitution, Kassel, 1899.

(12) Bauer, J.: Die konstitutionelle Disposition zu inneren Krankheiten, Berlin, 1921.

(13) Pearl, R.: Studies in Human Biology (especially chapter 10), Baltimore, 1924.
Later, numerous studies on constitution, Human Biol., 1929, *et seq.*

(14) Long, Esmond R.: Acquired and constitutional factors in resistance to tuberculosis, Tr. Nat. Tuberc. A. 31st meeting, 1935.

(15) Beneke, R.: Die anatomischen Grundlagen der Konstitutionsanomalien, 1878.
Konstitution und konstitutionelles Kranksein des Menschen, Marburg, 1881.

(16) Stiller, B.: Die asthenische Konstitutionskrankheit, Stuttgart, 1907.
Grundzüge der Asthenie, Stuttgart, 1916.

(17) Lurie, Max B.: Heredity, constitution and tuberculosis, An experimental study, Supplement, Am. Rev. Tuberc., September, 1941.

(18) Long, Esmond R.: Constitution and related factors in resistance to tuberculosis. Especially: Experimental studies on heredity in tuberculosis, Arch. Path., 1941, *32*, 122–162 and 286–310.

(19) Wallgreen, Arvid: From childhood infection to adult type of pulmonary tuberculosis, Acta tuberc. Scandinav., 1936, *10*, 321.

(20) Frost, W. H.: The outlook for the eradication of tuberculosis, Am. Rev. Tuberc., 1935, *32*, 642.

(21) Landé, Kurt E., and Wolff, Georg: 1941. Frequency of tuberculous lesions at autopsy, Some epidemiological inferences, Ibid., 1941, *44*, 223.

(22) Pearson, K.: Tuberculosis, heredity and environment, London, 1912.

(23) Wolff, G.: Tuberculosis mortality and industrialization, Am. Rev. Tuberc., 1940, *42*, 1–27 and 214–242.

UNDIAGNOSED PULMONARY TUBERCULOSIS IN ELDERLY PERSONS[1,2]

RAYMOND E. MILLER AND BEATRICE HENDERSON

One of the greatest deficiencies in tuberculosis control programs has been the failure to make sufficient use of case-finding techniques in discovering the elderly person with undiagnosed pulmonary tuberculosis. There is much evidence that the older individual suffering from this disease frequently escapes recognition, and may act as a spreader of tuberculosis in the community for many years. Myers (1) has stated that, in persons over fifty years of age, the prevalence of communicable pulmonary tuberculosis is higher than at any other age period. The importance of this type of case has also been emphasized by Godfrey (2) who wrote, "the early diagnosis of a late case that is spreading tubercle bacilli under the guise of having asthma or chronic bronchitis is more important than treating a minimal case that is non-infectious. That we are not finding these spreaders is evident from the wide dissemination of the tubercle bacillus, the frequency of appearance of active, sporadic cases, and the small percentage of older household contacts who are examined. . . . The higher age groups are where the cases are found, and it is among these that we are examining fewest."

Other writers, among them Jennings (3), Collis (4), Freeman and Heiken (5), Rich (6), Lander (7) and Hatfield (8), have also noted the frequency of tuberculosis in the aged, and have suggested that more attention be paid to case-finding in this group.

There are various reasons for the comparative neglect of the elderly person in tuberculosis control programs. Tuberculosis has commonly been thought of as a disease of youth, and consequently the majority of case-finding efforts have been directed toward those of younger years. Also, as Bloch (9) has noted, it is a great deal easier to obtain funds for tuberculosis control programs in young prople than in those of advanced age. In addition, the methods most commonly used in tuberculosis case-finding do not ordinarily succeed in reaching the older section of the population.

Occasionally the elderly spreader of tuberculosis may be found by contact examination technique: that is to say, examination of all those individuals who are known to have had intimate contact with a newly discovered case of tuberculous infection in a younger person. Experience has shown, however, that it is often difficult—if not impossible—to obtain the examinations of all those individuals. This is particularly true of the older person who frequently refuses examination either because of apathy, or because of fear that something will be

[1] From the Tuberculosis Clinic of the Kips Bay-Yorkville District Health Center of the New York City Department of Health, and the Department of Public Health and Preventive Medicine, Cornell University Medical College, New York, New York.

[2] Aided by a grant from the International Health Division of The Rockefeller Foundation.

found which will force him to change his mode of life. Godfrey (2), surveying the records of 17 counties in upstate New York, found that the percentage of contacts examined was highest in the five to nine year age group, and that the percentage examined dwindled steadily with increasing age. In the cases studied, 43.1 per cent of contacts under forty years of age were examined, while only 14.4 per cent of contacts over forty received attention.

Sometimes the elderly person having tuberculosis will be found through examination of those with pulmonary symptoms. Older people, however, are apt to ascribe their symptoms to a natural decline in health attending upon old age, or merely to an aggravation of a preëxisting chronic but minor illness. Consequently they fail to seek medical advice. If the major symptom is fatigue, they are especially unlikely to request a medical examination; for, as Rich (6) has stated, "not only do the aged engage in less physical exertion than do younger adults, but even in their normal state they are much more easily fatigued, and the contrast between the degree of fatigability in health and that after the onset of tuberculosis is much less noticeable than in younger age periods."

In addition, there are many elderly tuberculous individuals whose disease has become more or less stabilized. Such a person may be robust, well-nourished and present an appearance of complete health. Usually he has only minor symptoms and frequently he is able to work and to carry on a normal life. He often lives out his natural life span, dying, not of tuberculosis, but of some entirely unrelated disease. Unfortunately these apparently healthy people frequently expectorate large numbers of tubercle bacilli over long periods of time and, due to the fact that they are not suspected of being tuberculous, they are particularly dangerous sources of infection. Such cases are familiar to physicians in tuberculosis sanatoria, where they are usually labelled "good chronics." Similar cases which are at large in the community may be thought of as "bad chronics" from the point of view of public health.

The best method of finding the elderly spreader of tuberculosis would seem to be through the use of the mass X-ray survey. Up to the present time, however, this method has not been used widely among older groups. Bloch (9) has estimated that more than half the reports published on surveys in adults concern themselves with university students, hospital personnel and student nurses. The majority of other surveys have been made on industrial and racial groups containing only a relatively small percentage of persons above the age of forty.

Despite the fact that he is seldom discovered by any of the aforementioned methods of case-finding, the relative frequency with which the elderly phthisic occurs in the population should make him of the greatest concern to those interested in tuberculosis control. Mortality figures for the United States, as prepared by Dublin (10), show that the highest death rate from tuberculosis occurs in males from sixty-five to seventy-four years of age, and in females seventy-five and over. Mortality statistics for New York City, as shown in table 1, prepared from figures furnished us by Drolet (11), illustrate the fact that the decline in tuberculosis mortality since 1920 has been much greater in

the young than in the old, particularly in males. The phenomenal decrease in tuberculosis among younger persons of New York City during this twenty-year period may very well reflect the efficiency of the methods used for the prevention, detection and treatment of tuberculosis in this portion of the population. The persistently high mortality of the elderly may partially be due to the fact that the same degree of emphasis has not been placed on the control of tuberculosis in the latter group.

TABLE 1

Tuberculosis mortality among adult white persons

New York City, 1920 and 1940

AGE AND SEX	YEAR 1920		YEAR 1940		PERCENTAGE OF 1920 DEATH RATE
	Deaths	Rate	Deaths	Rate	
Male:					
20–24	329	135	52	18	13.3
25–34	787	149	231	36	24.2
35–44	877	203	367	64	31.5
45–54	800	267	481	94	35.2
55–64	404	256	415	146	57.0
65–74	138	226	197	137	60.6
75+	37	197	50	133	67.5
Female:					
20–24	440	153	100	31	20.3
25–34	685	129	193	28	23.3
35–44	441	110	153	27	24.5
45–54	244	88	104	22	35.1
55–64	124	79	77	27	34.2
65–74	76	109	61	37	33.9
75+	14	53	29	55	103.8

Notes: Rates per 100,000 population, for 1920 as of July first, for 1940 as of April first—the latter based on age and sex distribution as figured by U. S. Bureau of the Census on a 5 per cent sample. Deaths in 1920 include small number of "other colored" than Negro. Compiled from reports of Department of Health, City of New York, by G. J. Drolet, New York Tuberculosis and Health Association.

X-RAY SURVEY OF 3,414 PERSONS ON HOME RELIEF

As part of its case-finding program, the Kips Bay-Yorkville Chest Clinic, one of the New York City Department of Health tuberculosis clinics, has utilized its facilities and personnel to make roentgenograms of groups of apparently healthy individuals residing in the area served by the clinic. These efforts have been concentrated on those of low income, as mass X-ray survey studies by Edwards and his associates (12) have demonstrated the higher prevalence of tuberculosis in this portion of the population.

The survey described in this paper was undertaken as part of the New York City program, and in order to study the incidence of undiagnosed pulmonary tuberculosis at various age levels. The group examined consisted of those per-

sons residing in the area who were receiving Home Relief. This group contained persons of all ages. The survey was limited to those fifteen years of age and above, as previous surveys have shown the rarity of reinfection tuberculosis in children under fifteen. Known cases of tuberculosis, known contacts and persons who had had a roentgenogram of the chest within the preceeding six months were not included in the final figures.

Cut paper films, 14 x 17 inches in size, were used in standard X-ray equipment. The films were read independently by two members of the staff.

An analysis of the results of the survey is summarized in table 2, which shows the total number of persons examined in each age group, as well as the amount

TABLE 2

Age and sex distribution of chronic and significant pulmonary tuberculosis

AGE GROUP	MALES					FEMALES				
	Number examined	Chronic pulmonary tuberculosis	Per cent	Significant pulmonary tuberculosis	Per cent	Number examined	Chronic pulmonary tuberculosis	Per cent	Significant pulmonary tuberculosis	Per cent
15–19.9	133	0		0		134	0		0	
20–29.9	74	2	2.70	2	2.70	161	1	0.62	0	
30–39.9	192	11	5.73	5	2.60	314	9	2.87	5	1.59
40–49.9	257	30	11.67	17	6.61	347	17	4.90	6	1.73
50–59.9	365	44	12.05	22	6.03	418	35	8.37	10	2.39
60–69.9	350	50	14.29	17	4.86	450	49	10.89	8	1.78
70–79.9	116	20	17.24	5	4.31	84	9	10.71	3	3.57
80–84.9	9	2	22.22	0		10	2	20.00	0	
Total	1,496	159	10.63	68	4.55	1,918	122	6.36	32	1.67
Under 40	399	13	3.26	7	1.75	609	10	1.64	5	0.82
Over 40	1,097	146	13.31	61	5.56	1,309	112	8.56	27	2.06

and percentage of chronic and significant tuberculosis. These terms have been defined by Edwards (12) as follows:

"Chronic pulmonary tuberculosis . . . includes all lesions characteristic of the reinfection form of the disease. The reports in this series captioned chronic pulmonary tuberculosis include lesions adjudged as arrested as well as those of some clinical significance. . . . The term 'clinically significant' as used in these reports includes all cases in which the radiographic shadow indicates a lesion typical of a reinfection form of the disease varying from those obviously active, with associated constitutional symptoms and physical findings, to those without associated findings, but in which the stability of the lesion cannot be determined without periodic supervision."

In all, 3,414 persons were X-rayed; 42 per cent of these were native born whites; 57.7 per cent were foreign-born whites; while 0.3 per cent were Negroes, Puerto Ricans or Chinese. It will be noted from table 2 that 10.63 per cent of all males examined and 6.36 per cent of all females were found to have chronic

pulmonary tuberculosis; while 4.55 per cent of males and 1.67 per cent of females had significant tuberculosis. This table also shows the preponderance of all forms of reinfection tuberculosis in those of this group above the age of forty.

Each person with significant tuberculosis was recalled to the clinic for celluloid X-ray films, complete history and physical examination. When possible, sputum examinations were made, but when no sputum was obtainable a gastric analysis was done. It has been possible to maintain follow-up examinations over periods ranging from six months to twenty-one months in 93 of these cases. It was not possible to follow 7 patients for a sufficient length of time to arrive at a definite diagnosis, for the reasons listed below:

Uncoöperative: 2 patients
Moved, unable to locate: 2 patients
Moved, under care of private physician: 1 patient
Died of other causes: 2 patients

TABLE 3

Active pulmonary tuberculosis, home relief group

	MEN				WOMEN			
Age	Number	Number active	Per cent	Sputum positive	Number	Number active	Per cent	Sputum positive
15–19.9	133	0	0	0	134	0	0	0
20–29.9	74	1	1.35	0	161	0	0	0
30–39.9	192	1	0.52	1	314	2	0.64	0
40–49.9	257	5	1.95	0	347	0	0	0
50–59.9	365	7	1.92	5	418	2	0.48	0
60–69.9	350	6	1.71	5	450	2	0.44	1
70–79.9	116	1	0.86	0	84	2	2.38	1
80–84.9	9	0	0	0	10	0	0	0
Total	1,496	21	1.40	11	1,918	8	0.42	2

Of the 100 clinically significant cases, a total of 29 have proven to be active, as detailed in table 3. A diagnosis of activity was made on the basis of either of the following findings:

1: Change in the X-ray appearance of the lesion; either progression or regression.
2: Positive sputum.

DISCUSSION

Examination of the foregoing tables reveals that, in the group studied, all forms of reinfection pulmonary tuberculosis were more common in the elderly than in the young. Males showed a higher percentage of tuberculosis at all ages than did females.

The cases of tuberculosis which are most important from a public health point of view are those which are active and particularly those in which the sputum is positive. In this connection it will be noted that 12 of the 13 persons

who were found to have positive sputum were above the age of fifty. None of these 13 had marked symptoms at the time of discovery, and some of them—the "good chronics"—have remained relatively symptom-free during the period of almost two years of observation, even though they have continued to expectorate tubercle bacilli.

In such cases, the persons who would subsequently feel ill might be discovered only after a much longer time interval, during which they would have the opportunity to spread their disease. Those cases in which the symptoms have not become acute might remain undiagnosed indefinitely, unless they happen to be traced as sources of tuberculous infection in young people.

The cases which have been considered as either healed or arrested are not of immediate importance from a public health point of view. It is valuable, however, to discover them and keep them under observation, as they may become active in the future. This is particularly true in the cases of the unemployed, whose living conditions are often unfavorable and whose food intake is limited, or even inadequate. Another factor, which may precipitate a reactivation of disease in these arrested cases, is reëmployment at heavy work due to a scarcity of labor in the defense industries. It is thought that many of these persons with healed or arrested tuberculosis, whose disease remains quiescent during the comparative inactivity of unemployment, may have a breakdown when physical labor is resumed.

It is not known whether the higher incidence of tuberculosis in the elderly which we have encountered in a group of unemployed also occurs in elderly persons of higher income levels. Since mortality tables are prepared from deaths at all strata, it would seem possible that this may be the actual state of affairs. In any event, it is of the utmost importance to devote a greater portion of our efforts in tuberculosis case-finding to the discovery of the elderly individual with tuberculosis. This should be done without lessening case-finding measures in young persons, as the latter comprise a larger proportion of the population than do the elderly. Consequently, although the percentage of tuberculosis may be less in those of younger years, the absolute number of cases undoubtedly is greater.

More emphasis should be placed on the examination of all the possible sources of a newly diagnosed case of tuberculosis. Even when the older members of a tuberculous household appear to be in the best of health, they should be X-rayed. When a thorough search of the immediate family of an affected person fails to reveal the source of infection, further inquiries should be made as to the identity of those others with whom he has most frequent contact, and examination of these persons should be arranged.

More attention should be paid to the examination of those elderly persons with mild pulmonary symptoms, as these symptoms which the patient, and even his physician, often attributes to "chronic bronchitis," "asthma," or some other minor chronic pulmonary disorder of the aged may actually be due to tuberculosis.

The physician should also always suspect tuberculosis in all his elderly patients

who have even mild pulmonary symptoms, and should take the necessary steps to rule out this disease before making a final diagnosis.

As we have stated before, the most productive method of case-finding among the elderly would seem to be the X-ray survey of such population groups. The survey detailed in this paper serves to illustrate the value of such a procedure. Similar surveys which are concentrated on the older fraction of the population, and particularly on older males, would, we believe, disclose many unknown spreaders of tuberculosis who have been acting as reservoirs of disease in their communities.

SUMMARY

1. The results are presented of an X-ray survey of 3,414 unemployed adults in New York City.

2. This survey disclosed 281 individuals with previously unsuspected chronic pulmonary tuberculosis. Of this number, 100 were regarded as having significant pulmonary tuberculosis; of this latter group, 29 have shown definite evidence of activity, either positive sputum or change in the X-ray appearance of the lesion.

3. All forms of tuberculosis were more common in the older fraction of the group studied than in the younger. The cases of significant tuberculosis and those which have proven to be active were approximately three times as common in persons above forty as in those under that age. Twelve of the 13 cases showing positive sputum were above the age of fifty.

4. All methods of case-finding should be more vigorously employed in the search for tuberculosis in higher age groups. The X-ray survey, directed specifically toward elderly persons, is a particularly effective method of discovering tuberculosis in this group.

SUMARIO

1. Preséntase el resultado de un censo roentgenológico de 3,414 cesantes adultos en la ciudad de Nueva York.

2. Dicho censo reveló 281 individuos con tuberculosis pulmonar crónica previamente insospechada: en 100 se consideró que había tuberculosis pulmonar de cierta importancia, y 29 de ellos revelaron signos bien definidos de actividad, ya esputo positivo o modificación del aspecto roentgenológico de la lesión.

3. Todas las formas de tuberculosis fueron más comunes en las personas de mayor edad del grupo estudiado que en las más jóvenes. Los casos de tuberculosis significativa y los que resultaron activos fueron aproximadamente tres veces más frecuentes en las personas de más de 40 años que en las de menos de esas edad, y 12 de los 13 enfermos con esputo positivo tenían más de 50 años.

4. En la pesquisa de la tuberculosis en los grupos de mayor edad deben emplearse más enérgicamente todos los tres métodos de indagación. El censo roentgenológico encaminado específicamente hacia las personas de cierta edad, resulta en particular eficaz para descubrir la tuberculosis en este grupo.

REFERENCES

(1) MYERS, J. ARTHUR: The physician and tuberculosis, J. A. M. A., 1939, *113*, 189.
(2) GODFREY, EDWARD S., JR.: Epidemiology of tuberculosis. Principles of programs of tuberculosis associations, Am. Rev. Tuberc., 1941, *43*, 1.
(3) JENNINGS, F. L.: Tuberculosis among older age groups, Journal-Lancet, 1938, *58*, 160.
(4) COLLIS, E. L.: Tuberculosis and influenza in relation to World War 1914–1918, Tubercle, Supplement, 1940, *21*, 3.
(5) FREEMAN, JOSEPH T., AND HEIKEN, CHARLES A.: The geriatric aspect of pulmonary tuberculosis, Am. J. M. Sc., 1941, *202*, 29.
(6) RICH, ARNOLD RICE: The influence of age-determined factors on the development of tuberculosis, Minnesota Med., 1938, *21*, 745.
(7) LANDER, F. P. LEE: Senile pulmonary tuberculosis, Brit. J. Tuberc., 1936, *30*, 183.
(8) HATFIELD, W. H.: Case-finding, Am. Rev. Tuberc., 1940, *41*, 784.
(9) BLOCH, ROBERT G.: Case-finding in tuberculosis, Ibid., 1941, *43*, 213.
(10) DUBLIN, LOUIS I.: Decline in tuberculosis. Present death rates and the outlook for the future, Ibid., 1941, *43*, 224.
(11) DROLET, G. J.: Private communication.
(12) EDWARDS, H. R.: Tuberculosis case-finding. Studies in mass surveys, Supplement to Am. Rev. Tuberc., June, 1940.

TUBERCULOSIS IN EXPOSED POPULATIONS[1]

HILBERT MARK[2]

The rapid expansion of Public Health activities in the numerous medical fields, as is evident to-day, has brought with it the frequent use of the word "control." In the case of tuberculosis, the literature is full of articles expounding this or that theory of so-called successful control procedures. Certainly a sufficient number of well controlled studies have been made at various age levels of special population groups to indicate to us the best known procedure to follow in the ultimate eradication of the disease. However, before eradication can be considered, the epidemiology of the disease must be well understood and also closely followed.

The modern concept of the spread of tuberculosis from an open case to a susceptible person dates back to pre-Koch times. Hippocrates, Sylvius and others recognized the infectious nature of tuberculosis long before Koch discovered the tubercle bacillus. Studies in 1912 by Lampson (1), then epidemiologist for the Minnesota State Department of Health, showed that the intimacy and length of exposure are the determining factors in infection. The more recent work of Asserson (2), McPhedran and Opie (3), Zachs (4), Edwards (5) and others (6, 7, 8, 9, 10) further confirms the fact that the frequency of infection and disease in any age group varies directly with the degree and length of exposure to open tuberculosis.

Brailey (11), in an excellent study, showed that familial association with sputum-positive cases carries a risk of infection twice as great as similar association with negative-sputum cases. Her study was limited to households in which there was or had been a definitely diagnosed case of pulmonary tuberculosis in an adult and dealt only with individuals entering the household under fifteen years of age and were followed only to twenty years of age.

Elimination of open tuberculosis from the community means ultimate eradication of the disease. Where there is no seed, there can be no harvest regardless of the type of the soil. Obviously any program for tuberculosis control must include finding not only the infectious cases but also and especially those in the noncontagious or minimal stage of the disease.

From a biological point of view it is not necessary to find every case of tuberculosis. Reduction of the number of cases in any community to a minimum will in time through natural processes of chance be sufficient to bring about the desired results.

Frost (12) found through statistical analysis of available epidemiological data that "it is only necessary that the rate of transmission be held permanently

[1] Read before a joint meeting of the Mississippi Valley Trudeau Society and the Mississippi Valley Conference on Tuberculosis, Columbus, Ohio, October 3, 1941.

[2] Epidemiologist, Minnesota State Department of Health, Division of Preventable Diseases, Minneapolis; on military leave.

below the level at which a given number of infection-spreading cases succeed in establishing an equivalent number to carry on the succession." This is termed "biological balance." This same thought of biological balance was recently emphasized by Godfrey (13).

Since the first mass tuberculosis-testing programs were conducted among school children, it may be well to consider that group first. A review of recent studies among school children reported by sixteen investigators[3] reveals that among a total of about 635,000 school children of all ages, including some in colleges, the percentage of yield of active cases varied from 0.08 to 1.6 per cent. The latter percentage was found in a college group and included some active primary tuberculosis. Lyght (28) reported that less than 1.0 per cent of all university and college students tested had demonstrably active tuberculosis.

Based on their own observation, Edwards (29) and Godfrey (13) concluded that case finding in school children was expensive and comparatively unproductive. Godfrey goes so far as to say that the "promiscuous tuberculin-testing of school children is a waste of time, money and effort." The cost of finding a reinfection case of tuberculosis among school children was found by Pleyte (27) to be $1400, and by Zachs (4), $1430.

In 1934–1935 the writer conducted a survey for the Minnesota State Sanatorium of seven rural Minnesota counties. The survey included Mantoux testing of school children and adults, follow-up of reactors' families and follow-up of families of reported tuberculosis cases and deaths. In all 20,720 persons were tested. The Mantoux and X-ray results of this survey are given in table 1.

A dilution of 1:1,000 Old Tuberculin was used and the negative reactors were not retested. A total of 2,939 persons reacted, of whom 1,312 gave a history of family exposure. In this "intimately exposed" group, 21 were found to have evidence of pleurisy, 4 bone and joint tuberculosis and 92 reinfection type lesions, a yield of 7.1 per cent. In the "casually exposed" group of 1,627 reactors, 40 revealed pleurisy, and only 17 were found to have reinfection type tuberculosis. This is a yield of 1.0 per cent. In both groups pleurisy was not included in computing the percentages.

It is evident from the above table that persons living in a tuberculous environment have a significantly greater case risk than those who are exposed casually, that is, outside of the home, the exposure usually being to an unknown source. The results of this survey again confirm previous reports of the significance of degree of exposure. Obviously any case-finding program must first concern itself with that group of persons in whom we expect to find the greatest number of cases at the least cost of time, money and effort.

A word about special population studies: Edwards (29) has shown that, when special population groups are carefully chosen, a sufficient number of cases will be found to make such studies of value. Before recommending special population group studies, however, one should take into consideration the social and industrial conditions as well as the morbidity and mortality

[3] See Bibliography, references 4, 9, and 14 through 27.

rates of the community. Mass studies of whatever type should be carefully considered from the standpoint of effort, cost and yield. Certainly the first action in the control of tuberculosis must be the isolation of the infectious case and the examination of all intimately exposed persons. When such work has not been adequately accomplished in a community, it will be noted that most

TABLE 1

AGE	MANTOUX			X-RAY				
	Negative	Positive	Per cent Positive	Negative	Calcified Primary	Pleurisy	Reinfection	Bone
Intimately Exposed								
0 to 4	43	26	77.6	11	5	0	0	2
5 to 14	270	320	54.2	107	120	0	4	2
15 to 24	164	290	63.8	97	121	3	14	0
25 to 44	119	376	75.9	110	133	8	43	0
45-up	60	190	76.0	49	75	8	17	0
Unknown age	33	110	76.9	38	35	2	14	0
Total.....	689	1,312	65.6	412	489	21	92	4
Casually Exposed								
0 to 4	477	13	2.7	3	1	0	0	0
5 to 14	11,054	482	4.1	107	172	2	1	0
15 to 24	2,879	415	12.6	117	168	7	3	0
25 to 44	737	336	31.3	95	174	9	4	0
45-up	152	111	42.2	38	41	12	6	0
Unknown age	1,793	270	13.1	112	111	10	3	0
Total.....	17,092	1,627	8.7	472	667	40	17	0
Total								
0 to 4	520	39	6.9	14	6	0	0	2
5 to 14	11,324	802	6.6	214	292	2	5	2
15 to 24	3,043	705	18.8	214	289	10	17	0
25 to 44	856	712	45.4	205	307	17	47	0
45-up	212	301	58.5	87	116	20	23	0
Unknown age	1,826	380	17.2	150	146	12	17	0
Total.....	17,781	2,939	16.5	884	1,156	61	109	4

of the cases found in school children or special population groups will be those who have been intimately exposed to an infectious case in the home.

For example, in 1938 Fischer (14), Health Officer of Duluth, Minnesota, conducted a compulsory case-finding program in a junior high school, in which the entire school population of 1,238 students was tested. Three reinfection cases were found, and all 3 cases had a positive family history.

With the dramatic and popular appeal of special tuberculosis case-finding,

one is apt to ignore the basic principle of the epidemiology of tuberculosis, which bears repetition, and is that tuberculosis develops from tuberculosis. The longer and the more intimate the exposure, the greater the risk of the exposed person regardless of age level.

In 1940 Dr. L. J. Webster (30), Superintendent, Otter Tail County Sanatorium, Battle Lake, Minnesota, and the writer conducted a survey in a rural Minnesota county of some 50,000 population. As one part of the survey it was planned to examine all members of families in which there was or had been a case of tuberculosis. A visit was made to the home of the reported case or his closest kin and appointment was made for the contacts to appear at a Mantoux clinic. Adults were given initial Mantoux tests of 1:10,000 dilution OT, and if negative in forty-eight hours, the tests were repeated with a dilution of 1:100 OT. It was felt that by this method, the weaker dilution followed by the stronger dilution, painful local reactions which would occur with an initial 1:1,000 dilution would be prevented. All children under twelve were given initial tests with a dilution of 1:1,000 OT and most of them were not retested. The tuberculin used was freshly prepared for each clinic and furnished by the Minnesota Department of Health. All those found to have positive Mantoux reactions were given appointments for X-ray films at the Sanatorium. All films were sent to the University Hospital for interpretation by its roentgenological staff.

In all, there were 698 families with positive tuberculosis histories, in which 3,867 members were found residing in Otter Tail County. Of these, 1,522 presented themselves for Mantoux tests, and 765, or 50.2 per cent, were positive. In addition to the reactors, there were 403, who either had had previous positive Mantoux reactions or who did not take the original test, who presented themselves at the Sanatorium for X-ray films, so that altogether 1,168 family contacts were X-rayed. Fifty-eight individuals were found to have reinfection tuberculosis not previously known, of whom 14 had active disease requiring immediate sanatorium care. Six, or 45 per cent, of the active cases were minimal; 3, or 21 per cent, were moderately advanced; and 5, or 35 per cent, were far advanced. In addition to the new cases discovered, 21 old cases were found to have reactivated disease with positive sputum.

The cost of the survey is given in table 2. No charge was made for interpretation of X-ray films by the University of Minnesota Hospital Staff. Included in the cost, however, is a proportionate share of the salaries of all regular Sanatorium employes who devoted part time to the survey, though their salaries were continued by the Sanatorium.

The cost of finding a new reinfection type case of tuberculosis, whether active or inactive, was $96.05. If one considers only the 14 new cases of active reinfection tuberculosis and the 21 old reactivated cases, the cost per active case found was $159.14. Compare this cost with those reported by Pleyte and Zachs, given above. When the economy of effort is also taken into consideration, one can understand why other investigators believe that promiscuous tuberculin testing of population groups not carefully selected is a waste of time,

money and effort, in the face of the need for more concentrated studies of exposed population.

TABLE 2

Cost of survey

	SOURCE OF FUNDS		TOTAL
	State and Federal	County and Local	
Salaries	2,686.99	1,564.24	4,796.50
Travel	545.27		
Supplies:			
X-ray and chemicals	678.53		678.53
Office and miscellaneous	20.82	75.00	95.82
Total	3,931.61	1,639.24	5,570.85

SUMMARY

1. Well controlled studies made at various age levels of special population groups by many workers indicate the best procedure to follow in the ultimate eradication of the disease; namely, the isolation of the infectious case and the examination of all intimately exposed contacts.

2. The frequency of infection and disease in any age group varies directly with the degree and length of exposure to open tuberculosis.

3. Any program for tuberculosis control must include finding not only the infectious cases but also and especially those in the noncontagious or minimal, stage.

4. Studies of special population groups may be of value but any mass study of whatever type should be carefully considered from the standpoint of effort, cost and yield.

5. A review of recent studies among school children, reported by sixteen investigators, reveals that among a total of about 635,000 school children of all ages, including some college students, the percentage of yield of active cases varies from 0.08 to 1.6 per cent. The latter percentage was found in a college group.

6. Reference is made to other workers who have concluded that case-finding in school children is expensive and comparatively unproductive.

7. A survey of seven rural Minnesota counties is reported, in which 20,720 school children and adults were studied. Persons who were intimately exposed showed a much greater incidence of disease than did those who were only casually exposed.

8. Another county survey is reported in which efforts were made to find and examine every member of 698 families in which there was or had been a case of tuberculosis. Of those tuberculin tested, 50.2 per cent reacted positively. Fourteen new active cases and 21 old reactivated cases were found. The cost

of finding each of these cases was $159.14. This figure is considerably less than that reported by other workers in making school surveys.

SUMARIO

1. Estudios comprobados realizados a varias edades de grupos especiales de la población por muchos investigadores, indican el mejor procedimiento que debe seguirse para la erradicación definitiva de la enfermedad; a saber, el aislamiento de los casos infecciosos y el examen de todos los contactos expuestos íntimamente.

2. La frecuencia de la infección y de la enfermedad en cualquier grupo etario varía directamente en razón a la intensidad y duración de la exposición a la tuberculosis abierta.

3. Todo plan de lucha antituberculosa debe comprender el descubrimiento no sólo de los casos infecciosos, sino también y en particular los que se encuentran en el período mínimo o no contagioso.

4. Los estudios de grupos especiales de la población pueden ser útiles, pero todo estudio colectivo de cualquier género que sea, debe ser cuidadosamente estudiado desde el punto de vista del esfuerzo, el costo y el rendimiento.

5. Un repaso de recientes estudios entre los escolares, comunicados por dieciséis investigadores, revela que entre un total de unos 635,000 escolares de todas las edades, incluso algunos estudiantes universitarios, el porcentaje de casos activos descubiertos varía de 0.08 a 1.6 por ciento. Este último porcentaje correspondió a un grupo universitario.

6. Discútense las afirmaciones de otros investigadores que han deducido que la pesquisa de casos en los escolares resulta costoso y comparativamente estéril.

7. Preséntase un censo de siete distritos rurales del Estado de Minnesota, en que se estudió a 20,720 escolares y adultos. Las personas íntimamente expuestas revelaron un coeficiente mucho mayor de enfermedad que las que sólo se expusieron de cuando en cuando.

8. Preséntase otro censo de un distrito en que se hicieron esfuerzos para descubrir y examinar a todos los miembros de 698 familias en que había o había habido algún caso de tuberculosis. De los comprobados con tuberculina, reaccionaron positivamente 50.2 por ciento. También se descubrieron catorce casos activos nuevos, y veintiuno reactivados viejos. El costo de descubrir cada uno de estos casos fué $159.14, lo cual es mucho menor que lo comunicado por otros técnicos que verificaron censos escolares.

BIBLIOGRAPHY

(1) Lampson, H. G.: The spread of tuberculosis; report on the spread of infection in certain tuberculous families in five counties in Minnesota, Pub. Health Rep., 1915, *30*, 75.

(2) Asserson, M. A.: Study of tuberculosis in infants, Tubercle, 1928, *9*, 323.

(3) McPhedran, F. M., and Opie, E. L.: The spread of tuberculosis in families, Am. J. Hyg., 1935, *22*, 565.

(4) Zachs, David: What we have learned from the ten year program in Massachusetts, New England J. Med., 1931, *204*, 1037.

(5) EDWARDS, H. R.: Case-finding; a method in the control of tuberculosis, Illinois M. J., 1938, *74*, 148.
(6) DOWNES, JEAN: A study of the risk of attack among contacts in tuberculous families in a rural area, Am. J. Hyg., 1935, *22*, 731.
(7) BLOCH, R. G.: Case-finding in tuberculosis, Am. Rev. Tuberc., 1941, *43*, 213.
(8) HATFIELD, W. H.: Case-finding, Ibid., 1940, *41*, 784.
(9) KORNS, J. H.: Tuberculosis among children and young people in Cattaraugus County, N. Y., Am. J. Pub. Health, 1938, *28*, 167.
(10) PLUNKETT, R. E., WEBER, G. W., SIEGAL, WILLIAM, AND DONK, ROSE R.: Development of tuberculosis in a controlled environment, Ibid., 1940, *30*, 229.
(11) BRAILEY, MIRIAM: A study of tuberculous infection and mortality in the children of tuberculous households, Am. J. Hyg., Sect. A, 1940, *31*, 1.
(12) FROST, W. H.: How much control of tuberculosis? Am. J. Pub. Health, 1937, *27*, 759.
(13) GODFREY, E. S., JR.: Epidemiology of tuberculosis, Am. Rev. Tuberc., 1941, *43*, 1.
(14) FISCHER, M. M.: Special report, 1938.
(15) Nopeming Sanatorium, Minnesota: Report of X-ray findings of school children at Esko's Corner, 1941.
(16) AYLING, WM. E.: Value of tuberculin skin tests in school program, New York State J. Med., 1939, *39*, 1463.
(17) BRALEY, W. N.: A tuberculin testing program in a school system of about 10,000 pupils, Health Department, City of Highland Park, Michigan, 1940.
(18) SUNDBERG, R. H.: Pulmonary tuberculosis from public health standpoint, Dis. of Chest, 1940, *6*, 8.
(19) RABINOWITZ, LOUIS, ROGERS, E. J., AND SLOCUM, H. W.: Tuberculosis survey in Vermont, Am. Rev. Tuberc., 1939, *40*, 435.
(20) JAMES, E. S.: Tuberculin survey of school children, Ibid., 1939, *40*, 306.
(21) MCCAIN, P. P.: Value of tuberculin test, J. Florida M. A., 1939, *26*, 279.
(22) EDWARDS, E. P.: The tuberculin reactor and tuberculosis control, Jour. Lancet, 1939, *59*, 126.
(23) EDWARDS, H. R.: Twentieth century case-finding, Ibid., 1938, *58*: 156.
(24) LEGGETT, ELIZABETH A., AND CALLAHAN, F. F.: Studies on the incidence of tuberculous infection, Am. Rev. Tuberc., 1931, *24*, 113.
(25) MARIETTE, E. S.: Early diagnosis campaign the rural Hennepin County plan, Minnesota Med., 1940, *23*, 471.
(26) PLUNKETT, R. E.: Case-finding, Am. Rev. Tuberc., 1939, *39*, 256.
(27) PLEYTE, A. A.: Finding tuberculosis among apparently healthy adults, Tr. Nat. Tuberc. A., 1937, *33*, 176.
(28) LYGHT, C. E.: Tuberculosis case finding among American college students, Minnesota Med., 1940, *23*, 465.
(29) EDWARDS, H. R.: Tuberculosis case-finding, Studies in mass surveys, Supplement to Am. Rev. Tuberc., June, 1940.
(30) WEBSTER, L. J.: Preliminary report of the special Otter Tail County tuberculosis survey, summer, 1940, Minnesota Med., 1941, *24*, 145.

A TUBERCULOSIS CASE-FINDING DEMONSTRATION IN SAN JOSÉ, COSTA RICA[1]

C. W. WELLS

Specialists in the detection of tuberculosis have long recognized the need for a technique of group diagnosis that would be rapid, economical and reasonably accurate. The literature contains many reports of surveys which have had as their principal object the uncovering of new cases of the disease. In these surveys reliance has been placed to a considerable extent on tuberculin screening, supplemented by film examination of positive reactors. This is expensive. This paper describes the technique employed and the results in a tuberculosis case-finding demonstration in San José, Costa Rica, in which a fluoroscope was used as the examining instrument. Examination of as large a number of persons as possible in a given time was considered desirable. The survey was begun in January, 1940, and terminated at the end of April, 1941; actually, however, the study occupied only about ten and one-half months.

A section of San José, comprising 71 city blocks and containing a population of 20,125, was designated the census area. It comprised 61 blocks of the slum district, and 10 blocks populated largely by the middle class. During the course of the survey, 13 stations were established in different localities in order to bring the diagnostic facilities near to the homes of the people in the census area.

To permit fluoroscopic examinations without aid of a dark room, a special hood of light-weight material was attached to the fluoroscope frame and provided with a suitable cap to fit over the head of the examiner. This contrivance proved exceptionally satisfactory.

The routine procedure comprised a fluoroscopic examination of the chest, supplemented by a roentgenogram on regular size film, paper or celluloid, of all positive or suspicious cases. Such cases were immediately referred to the Government Tuberculosis Dispensary, where other diagnostic measures were instituted and follow-up examinations were conducted. The final diagnosis was based upon the combined findings of the dispensary and mobile unit. Interest centered chiefly on the results obtained in the census or demonstration area, but it was not confined to that region. As a result of newspaper, radio and church publicity, many individuals living elsewhere reported at the various stations, voluntarily seeking examination; 6,876 such persons were examined, in addition to 2,157 grade and high-school children and 275 policemen. In the census area, 18,452 persons were examined, making a total of 27,760 examinations. About 2 per cent of all fluoroscopic examinations were followed by radiographic diagnosis by the mobile unit. The results are given in four tables: table 1, referring to

[1] The studies and observations on which this paper is based were conducted with the support and under the auspices of the International Health Division of the Rockefeller Foundation and the Secretaría de Salubridad Pública y Protección Social of the Government of Costa Rica.

the slum census area; table 2, to the middle-class census area; table 3, to individuals who lived outside the census areas; table 4, to school children and policemen.

In the poorer section the average number of persons per family was found to be 5.94; in the middle-class district, only 4.66. The average number of persons per room in the two districts did not differ materially, being 1.45 and 1.54, respectively.

The population of the census area in the so-called slum district was 14,361, 56.1 per cent of whom were females. Of this total, 13,184 persons, or 91.8 per cent, reported for examination. Degree of coöperation varied considerably with age. Among those over sixty years of age, 83.2 per cent were examined, whereas

TABLE 1

Results of fluoroscopic and X-ray examinations of the population in 61 city blocks, constituting slum districts in San José, Costa Rica

AGE	SEX	TOTAL POPULATION	NUMBER EXAMINED	PER CENT OF POPULATION EXAMINED	RESULTS OF EXAMINATIONS									NUMBER OF ACTIVE CASES PREVIOUSLY KNOWN (40.1 PER CENT)
					Healed primary lesions	Caseous mediastinal lymph nodes	Latent apical	Pleural adhesions	Diagnosis incomplete	Pulmonary tuberculosis				
										Minimal	Moderately advanced	Far advanced	Per cent pulmonary tuberculosis	
0–14	M	2,449	2,341	95.6	80	3			1	6	0	0	0.3	0
	F	2,637	2,525	95.7	61	6			1	5	0	0	0.2	0
15–29	M	1,918	1,702	88.7	115		1	1	1	14	2	2	1.1	10
	F	2,714	2,531	93.3	101		3	1	5	4	3	2	0.4	4
30+	M	1,932	1,648	85.3	125		9	2	4	18	8	3	1.8	13
	F	2,711	2,437	89.9	142		21	2	9	25	14	6	1.8	18
Total	M	6,299	5,691	90.3	320	3	10	3	6	38	10	5	0.9	23
	F	8,062	7,493	92.9	304	6	24	3	15	34	17	8	0.8	22
Total.....		14,361	13,184	91.8	624	9	34	6	21	72	27	13	0.85	45

children from five to nine years were reached to the extent of 97.7 per cent; 89.7 per cent of persons over fifteen years of age responded. In every age group, excepting children under four, the response of females exceeded that of males.

No significance should be attached to the number or percentage of healed or calcified tuberculous lesions discovered; as a rule, such lesions were noted only when exceptionally prominent. Chief attention was concentrated on the detection of lesions which might prove to be significant upon further study and examination. On this basis the occurrence of active tuberculosis, including cases with caseous lymph nodes, was found to be 0.9 per cent among those examined. Excluding the 9 cases of lymph node involvement, 64.3 per cent of the cases were

TABLE 2

Results of examinations of the population in 10 city blocks, representing middle class district in San José, Costa Rica

AGE	SEX	TOTAL POPULATION	NUMBER EXAMINED	PER CENT OF POPULATION EXAMINED	RESULTS OF EXAMINATIONS									NUMBER OF ACTIVE CASES PREVIOUSLY KNOWN (37.0 PER CENT)
					Healed primary lesions	Caseous mediastinal lymph nodes	Latent apical	Pleural adhesions	Diagnosis incomplete	Pulmonary tuberculosis				
										Minimal	Moderately advanced	Far advanced	Per cent pulmonary tuberculosis	
0–14	M	991	956	96.5	69	1	0	1	1	1	0	0	0.1	0
	F	1,176	1,140	96.9	69	1	0	0	0	0	0	0		0
15–29	M	678	588	86.7	105	0	0	1	0	1	2	0	0.5	1
	F	1,074	989	92.1	159	0	0	1	0	4	4	0	0.8	5
30+	M	748	609	81.4	83	0	4	1	1	2	2	0	0.7	1
	F	1,097	986	89.9	152	0	3	2		5	6	0	1.1	3
Total	M	2,417	2,153	89.1	257	1	4	3	1	4	4	0	0.4	2
	F	3,347	3,115	93.1	380	1	3	3	1	9	10	0	0.6	8
Total.....		5,764	5,268	91.4	637	2	7	6	2	13	14	0	0.5	10

TABLE 3

Results of examinations of persons living outside census areas, San José, Costa Rica

AGE	SEX	NUMBER EXAMINED	RESULTS OF EXAMINATIONS								NUMBER OF ACTIVE CASES PREVIOUSLY KNOWN (41.6 PER CENT)
			Healed primary lesions	Caseous mediastinal lymph nodes	Latent apical	Pleural adhesions	Diagnosis incomplete	Pulmonary tuberculosis			
								Minimal	Moderately advanced	Far advanced	
0–14	M	1,163	30	4			1	3			1
	F	1,137	20	1			5	4			1
15–29	M	1,439	67		1	4	2	11	4	1	8
	F	1,073	38				2	5	1	2	4
30+	M	1,128	68			1	6	10		4	7
	F	936	40		2		3	8	7		4
Total	M	3,730	165	4	1	5	9	24	4	5	16
	F	3,146	98	1	2		10	17	8	2	9
Total.....		6,876	263	5	3	5	19	41	12	7	25

minimal, 24.1 per cent moderately advanced, and 11.6 per cent far advanced. In persons over fifteen years of age the percentage of active tuberculous lesions was 1.2, of which 60.4 per cent were minimal. Only 0.2 per cent of those examined under fifteen years of age presented active lesions, excluding cases with lymph node involvement.

At the close of the survey the diagnosis of 21 persons in the slum area remained incomplete. The majority of these undoubtedly had insignificant lesions. The approximate actual occurrence of active tuberculosis in this population may be increased if further study and observation reveal active lesions in this group. Of

TABLE 4

*Results of examinations of 2,157 school children and 275 policemen, San José, Costa Rica**

AGE	SEX	NUMBER EXAMINED	RESULTS OF EXAMINATIONS							NUMBER OF ACTIVE CASES PREVIOUSLY KNOWN (23.7 PER CENT)
			Healed primary lesions	Caseous mediastinal lymph nodes	Pleural adhesions	Diagnosis incomplete	Pulmonary tuberculosis			
							Minimal	Moderately advanced	Per cent pulmonary tuberculosis	
0–14	M	1,041	47	3		1	2		0.2	
	F	703	63	1			2		0.3	1
15–19	M	393	18			1	1		0.2	1
	F	15	1							
20–29	M	111	5				4		3.6	
	F									
30+	M	169	10		1	2	2	2	2.4	1
	F									
Total	M	1,714	80	3	1	4	9	2	0.6	2
	F	718	64	1			2		0.3	1
Total.....		2,432	144	4	1	4	11	2	0.5	3

* All persons under twenty years of age and 5 in age group twenty to twenty-nine years were school pupils; none of the latter suffered from tuberculosis. All of the remaining persons were policemen.

the 112 active cases of tuberculosis diagnosed, only 45, or 40.1 per cent, were previously known.

Data shown in table 2, comprising results of examinations of a middle class population, differ little from the findings in the slum area with respect to the composition of the population by sex and the proportion of persons examined. A significant difference, however, was found in the percentage of active cases. Only 0.5 per cent of those examined were found to have active pulmonary tuberculosis. A slightly lower percentage of these active cases than of those found in the slum area were previously known to exist. The population in this district

(5,760) and the number examined (5,268) are sufficiently large to make the results significant. Again, a lower proportion of the cases in this area, 48.1 per cent, were minimal.

During the course of the survey, 6,876 persons living outside the census areas applied for diagnosis and were examined. The results are shown in table 3. As might be expected, a higher proportion, 54.2 per cent, were males; 66.1 per cent of those examined were fifteen years old and over, whereas in the census areas 62.3 per cent were in this age group. A total of 60 cases of active disease were diagnosed, or 0.9 per cent. Of these, 68.3 per cent were minimal, 20 per cent moderately advanced and 11.7 per cent far advanced. Of the persons with active lesions, 41.6 per cent were previously known to be affected. Active disease was found in 0.3 per cent of persons under fifteen years of age, and in 1.2 per cent of those fifteen years old and over.

By request, 2,157 school children living outside the census areas were examined. The number included boys from a large high school, which explains the excess of males over females. Five cases of active pulmonary tuberculosis were discovered, all minimal, only 2 of which were previously known to exist.

Circumstances incident to the connection of the equipment to a high-voltage line necessitated constant police surveillance. Two hundred and seventy-five of these guards were examined. Eight cases of active pulmonary tuberculosis were discovered, only one being previously known to exist. The proportion of cases, 2.9 per cent, is considerably higher than that found (1.6 per cent) among males of corresponding ages in the poorer census areas.

Discovery of a goodly proportion of early as well as advanced cases of tuberculosis among the general population, the existence of which were previously unsuspected, has been and continues to be one of the most important aspects of the tuberculosis problem. The survey conducted in Costa Rica was undertaken as a contribution toward this end. The capital, San José, has a population of about 65,000. During ten and one-half months, 27,760 persons, mostly inhabitants of the city, including about 75 per cent of its slum population, were examined for tuberculosis.

In our experience the fluoroscope has proved highly satisfactory; and others (1, 2, 3, 4) have been equally impressed. Its use can be strongly recommended as a valuable and reliable aid in tuberculosis case-finding, when experienced examiners are available.

The survey in Costa Rica produced several results which are of outstanding importance; the experience gained and the conclusions reached should prove helpful in the development of similar programmes elsewhere. The procedure usually followed in such surveys in the past has been to provide facilities for diagnosis in an existing tuberculosis dispensary or clinic; and by means of education and publicity to encourage individuals to report for examination. This method was followed by the writer in Jamaica (5); but in spite of strenuous effort by trained field workers and free transportation, only 78 per cent of the population responded. Edwards (6) reached only 25.4 per cent of the members of trade

unions by a similar procedure. It is believed that this method is ineffective in discovering a high percentage of active cases of tuberculosis. It is important to recognize that tuberculosis must be deliberately sought by bringing diagnostic facilities as near as possible to the homes of that section of the population in which the highest incidence of the disease is known to exist. These studies have demonstrated that more than 91 pr cent of the population can be examined when this procedure is followed.

The desirability of examining all persons, or at least a high percentage of them, in population areas selected for group diagnosis would probably be generally recognized by all tuberculosis workers. This study has demonstrated the importance of this goal. In every instance, from 10 to 15 per cent of the population in the immediate neighborhood of a diagnostic station remained unexamined when the unit was removed to another section of the city. Effort was continued to obtain the coöperation of individuals comprising the unexamined group. In the case of residents in 23 city blocks, a record was made to determine the prevalence of tuberculosis among those examined from the immediate neighborhood of a station and among those in the corresponding areas after the removal of the diagnostic unit. Considering only persons over fifteen years of age: among the 3,510 who readily came for examination, 19 cases of active tuberculosis were found, or 0.54 per cent. In the second group of 512 persons, 9 cases of active tuberculosis were found, or 1.75 per cent. This difference is highly significant, as shown by $X^2 = 9.56$ and $P = .002$, and demonstrates the importance of examining a high proportion of the population under investigation.

Experience in Costa Rica emphasized the necessity of catering to the convenience of the public, especially in regard to the hours for examination. At first examinations were made in the mornings and afternoons; this suited housewives and children, but failed to reach the working class, particularly adult males. To meet this situation, examinations were conducted two nights each week from seven to nine o'clock. The results confirm a belief that the coöperation of the general public in campaigns of this character will be in proportion to the consideration shown them in providing convenient hours for examinations.

Data are not available to determine the proportion of actual cases of tuberculosis existing in the census area. Undoubtedly some small minimal lesions were missed; this occurs whatever technique is employed. Frost (7) maintained that the efficient control of tuberculosis can be accomplished if from 85 to 95 per cent of all open cases in a community are known and adequately supervised. Douglas (8) expresses the same conclusion by stating that the goal should be the discovery of a "goodly proportion" of active cases. The San José studies are believed to have accomplished the ends advocated by these writers.

The value and importance of carrying the fight against tuberculosis directly to that portion of the population in which the disease may be expected to have a high incidence has been clearly demonstrated in this study; 139 cases of active disease were discovered by the procedure employed; 84 of these, or 60.4 per cent, were not previously known to exist. Further significance is given to the findings when the fact is realized that 85 of the cases, or 61.2 per cent, were in the minimal

stage when discovered. The degree of importance that should be attached to this latter finding will be recognized when comparison is made with the proportion of minimal cases on the registers of tuberculosis clinics and dispensaries, as revealed by official reports. In most instances, such records show that the percentage of minimal cases varies from 16 to 40 per cent.

SUMMARY

1. A tuberculosis survey conducted at San José, Costa Rica, over ten and one-half months during 1940-1941, involved the examination of 27,760 persons. A fluoroscope was used as a screen and was supplemented by X-ray photograph, laboratory examinations and further observation when necessary of all suspicious cases.

2. The census of the demonstration areas, 71 city blocks, comprised a population of 20,125, of whom 18,452, or 91.7 per cent, were examined.

3. A total of 9,308 other individuals living outside the demonstration areas were also examined.

4. Among the 18,452 persons examined in the census area, 139 cases, or 0.75 per cent, of active tuberculosis were discovered.

5. Of the 139 active cases in the census area, 84, or 60.4 per cent, were not previously known to exist; 61.2 per cent were minimal.

6. Among 6,876 examinees living outside the census area, 60 cases of active tuberculosis were discovered, or 0.87 per cent of the total. Of these, 68.3 per cent were minimal and 58.4 per cent were not previously known to exist.

7. The survey showed that among those who are less willing to submit to examination there is likely to be a significantly higher incidence of tuberculosis.

8. The survey demonstrated the possibility as well as the practicability of examining a high percentage of the population when a diagnostic service is taken to the people and when their time and convenience is considered.

9. Finally the results of this demonstration emphasize the importance of bringing diagnostic facilities as near as possible to the homes of individuals to be examined, and they are an incentive to tuberculosis workers in their search for new and early cases to evolve methods and procedures for case-finding which will appeal to the general public and elicit their full coöperation.

SUMARIO

1. Un censo tuberculoso llevado a cabo en San José de Costa Rica durante diez y medio meses en 1940–1941, comprendió el examen de 27,760 personas. Se empleó la roentgenoscopia como filtro, complementándola con roentgenogramas, exámenes de laboratorio y otras observaciones cuando parecían necesarias en los casos sospechosos.

2. En la zona de demostración (71 cuadras de la ciudad), el censo comprendió una población de 20,125, de los cuales se examinaron 18,454 (91.7 por ciento).

3. También se examinó a otros 9,308 individuos que vivían fuera de la zona de demostración.

4. Entre las 18,452 personas examinadas en la zona del censo, se descubrieron 139 casos, o sea 0.75 por ciento, de tuberculosis activa.

5. De los 139 casos activos de la zona del censo, 84, o sea 60.4 por ciento, eran desconocidos previamente, y 61.2 por ciento eran mínimos.

6. Entre las 6,876 personas examinadas fuera de la zona del censo, se descubrieron 60 casos, o sea 0.87 por ciento, de tuberculosis activa. De éstos, 68.3 por ciento eran mínimos, y 58.4 por ciento eran desconocidos antes.

7. El censo reveló que, entre las personas que muestran menos inclinación a someterse a examen, probablemente se encontrará un coeficiente significativamente mayor de tuberculosis.

8. El censo demostró la posibilidad, así como la factibilidad, de examinar a un elevado porcentaje de la población cuando se lleva el servicio diagnóstico al pueblo y se toma en cuenta la conveniencia del público.

9. Por fin, el resultado de la demostración pone de relieve la importancia de aproximar en todo lo posible los medios de diagnóstico a los hogares de los individuos que van a examinarse, constituyendo además un aliciente para los tisiólogos en su pesquisa de casos activos e incipientes la elaboración de técnicas y procedimientos dedicados al descubrimiento de los casos que interesen al público general y obtengan la plena cooperación de éste.

Acknowledgment is made of the coöperation of Dr. Raul Blanco Cervantes, Director of the Division of Tuberculosis of the Department of Health of Costa Rica, and of two of his assistants, Dr. Blanco Solis and Dr. Luis Munguia Alonso, in the conduct of the survey, as well as of contributions made by the Costa Rica Electric Light & Traction Co., Ltd., in service and loan of essential equipment.

REFERENCES

(1) Fellows, H. H.: Am. J. M. Sc., 1934, *188*, 533.
(2) Hetherington, H. W., and Israel, H. L.: Personal communication.
(3) Francisco, S. A., and Ongpin, C.: J. Philippine Islands M. A., 1935, *15*, 72.
(4) Bloch, R. G.: Am. Rev. Tuberc., 1941, *43*, 213.
(5) Wells, C. W., and Smith, H. H.: The Epidemiology of Tuberculosis, Kingston, Jamaica, B. W. I., Govt. Print. Office, 1938.
(6) Edwards, H. R., Preas, S., Downes, J., and Robins, A.: Am. Rev. Tuberc., 1941, *43*, 491.
(7) Frost, H. W.: Personal communication, 1936.
(8) Douglas, Bruce H.: Am. Rev. Tuberc., 1939, *40*, 621.

PROMIN IN EXPERIMENTAL TUBERCULOSIS[1]

Observations on Tuberculous Guinea Pigs before and after Treatment with Sodium P,P′-Diaminodiphenylsulfone-N,N′-Didextrose Sulfonate (Promin)

WILLIAM H. FELDMAN, FRANK C. MANN AND H. CORWIN HINSHAW

In previous reports (1, 2, 3) concerning the effect of sodium p,p′-diaminodiphenylsulfone-N,N′-didextrose sulfonate (promin)[2] on the expected course of experimentally induced tuberculosis, the results indicated that (*1*) this compound was capable of extending the survival time of the treated animals; (*2*) when treatment was started before or soon after the infection was introduced, the drug in many instances seemed to prevent the establishment of morbid changes characteristic of an experimental tuberculous infection; and (*3*) in instances in which the infective agent was introduced as long as six weeks before treatment was started, the anatomical character of the disease was markedly altered or recognizable signs of the disease were missing when the animals were examined at necropsy. The evidence that led to these conclusions was based largely on a comparison of the results obtained in the treated animals with the results obtained in the untreated controls.

That more impressive morphological evidence might be assembled which would indicate with reasonable certainty whether or not a deterrent effect had been exerted on a tuberculous process that was demonstrably present before treatment began, the following experiment was done.

METHODS

The guinea pigs used in this experiment totalled 51. All were young adult males and the weights of the animals varied from 450 to 500 g.

Each guinea pig was inoculated subcutaneously in the region of the sternum with 0.000,5 mg. of a seventeen-day-old subculture of human tubercle bacillus, H37RV.[3] Forty-two days later, each animal having reacted positively to an intracutaneous injection of tuberculin,[4] the animals were divided into two groups. Group 1 consisted of 31 animals and was considered as the untreated or control group. Group 2 consisted of 20 guinea pigs. These were to be the treated animals. Starting at the forty-second day and continuing daily thereafter for the duration of the experiment, each animal in group 2 received with the feed an estimated dose of 350 to 450 mg. of promin.[5]

[1] From The Mayo Foundation, Rochester, Minnesota.

[2] This drug, which was kindly supplied to us by Dr. A. E. Sharp of Parke, Davis & Co., has been designated by the manufacturer as "promin." Since an official designation for the drug has not been agreed on as yet, for the sake of brevity the compound will be referred to as promin throughout this report.

[3] The origin of this culture and the procedure followed in its artificial cultivation have been considered in a previous paper (3).

[4] Each animal was injected on the fortieth day with 0.02 to 0.03 cc. of 1:100 dilution of tuberculin (Gilliland).

[5] The basic feed supplied to each group of guinea pigs was the same and consisted of so-called rabbit chow to which was added 2.5 per cent corn syrup supplemented twice weekly with lettuce or fresh cabbage.

Biopsies: Forty-nine days after inoculation with tubercle bacilli laparotomy was performed under ether anesthesia on the 20 guinea pigs that constituted the treated group. Two days later 12 animals were taken at random from group 1 or the untreated controls and laparotomy was performed on each of them. It was the original intention to secure at the time of laparotomy a specimen for biopsy from the spleens. However, it was soon discovered that this was not a practical procedure, especially in those animals that had been receiving promin for one week prior to laparotomy. The spleens of most of these animals were markedly congested and were prone to serious haemorrhage at the slightest manipulation. The liver as a site for biopsy was selected instead.

Very little difficulty was experienced in obtaining specimens for biopsy from the livers of 18[6] of the animals in the treated group and 12 animals in the control group.[7] In most instances recovery was apparently uneventful. Of the 20 animals in the treated group on which operation was performed, 4 died either immediately or within a few days after the operation. Two of the fatilities were in animals in which attempts had been made to obtain specimens for biopsy from the spleen. In the other 2, biopsy of the liver had been performed. Subtracting the 4 guinea pigs that had died as a direct consequence of the surgical procedures there remained 16 animals in group 2 from which data could be obgained concerning the effect of the treatment with promin. All but one of the 12 control guinea pigs on which operation had been performed survived. The experiment was continued until the last of the animals in the untreated group had died. This occurred two hundred and twenty-four days after the animals had been inoculated with tubercle bacilli.

At the time of necropsy, attempts were made to culture tubercle bacilli from material of comparable amounts that was obtained from the livers of the animals in both groups that had been subjected previously to laparotomy.[8] Also there were preserved for subsequent microscopical study two large blocks of tissue from the liver, portions of the lung, the entire spleen and other tissues that were definitely or seemed likely to be tuberculous.

RESULTS

Survival time: As may be noted in figure 1, the first animal in the untreated group died forty-two days and the last of this group died two hundred twenty-four days after infection. The deaths of the other animals in this group were dispersed rather evenly during the period that intervened between the first and the last death.

At the two hundred twenty-fourth day when the last of the animals in the untreated group died there were still living in the treated group 13, or 81 per cent, of the 16 animals which constituted group 2 after the specimens for biopsy had been obtained. The 3 animals in the treated group that died did so one hundred three, one hundred twelve and two hundred twenty-three days, respectively, after being inoculated with tubercle bacilli.

Relative amounts of tuberculosis in untreated and in treated groups of animals: In figure 2 an attempt has been made to compare graphically the relative

[6] In 2 animals splenic biopsies were attempted.

[7] So as to minimize the risk of severe haemorrhage it was considered prudent to obtain only a small portion of tissue. These specimens measured 2 to 3 sq. mm.

[8] The culture procedure followed required that 2 cc. of each suspension prepared from the respective livers be treated with 5 per cent solution of oxalic acid and subsequently used to seed eight tubes of glycerinated egg-yolk-agar medium.

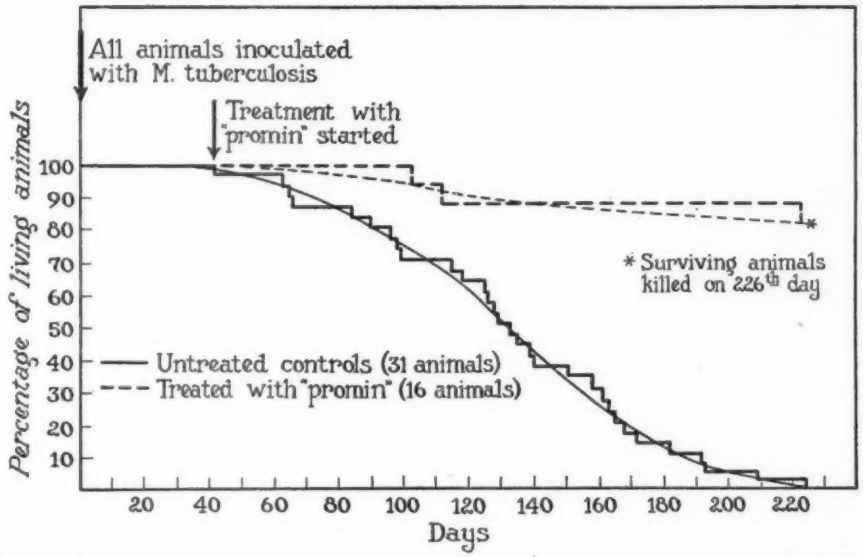


FIG. 1. Comparative survival time in days of tuberculous guinea pigs treated with promin and those not treated.

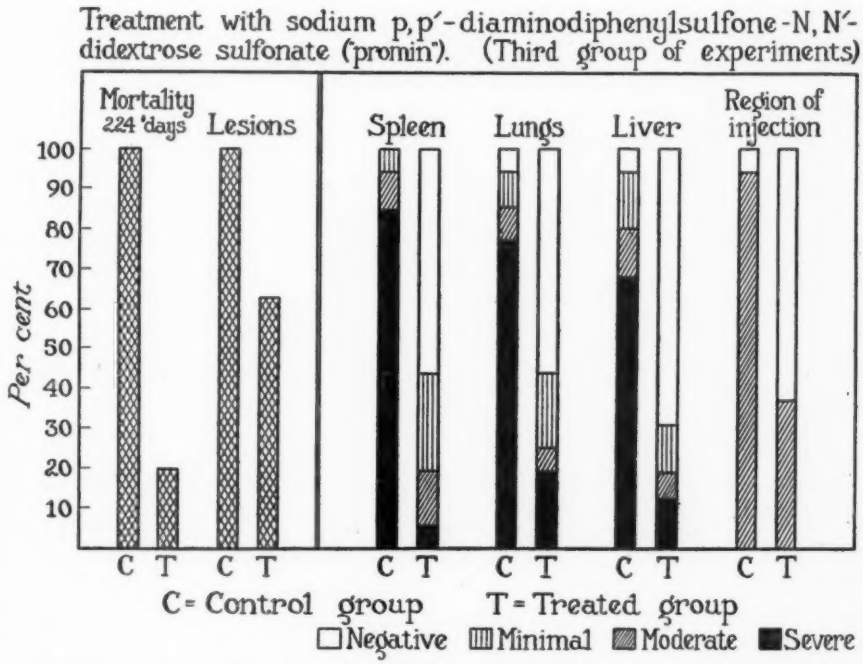


FIG. 2. Relative amounts of tuberculosis determined microscopically in treated and in untreated tuberculous guinea pigs.

amounts and the relative severity of the tuberculous disease in the principal organs and tissues of the animals comprising groups 1 and 2. Subsequently, studies revealed that lesions of tuberculosis were present in every one of the animals in the untreated group. Of the animals that had been treated with promin 6 were without demonstrable gross or microscopical sign of tuberculosis.

It seems significant that the spleens of all of the animals in the untreated group should have been definitely tuberculous with the disease severe in 84 per cent of the organs while the spleen of only one of the 16 animals in the treated group was the site of severe and extensive tuberculosis. This occurred in the guinea pig that died two hundred twenty-three days after inoculation and after having received promin for a total of one hundred eighty-one days. In this animal there was little if any evidence that the drug had influenced the extent and severity of the disease. At necropsy of this animal, lesions of tuberculosis were noted in the region of the subcutis where the bacteria had been injected and severe and destructive tuberculosis occurred in the lungs and liver in addition to the spleen.

As is shown graphically in figure 2, tuberculosis was found less often in the livers and lungs of the treated animals than in those that were not treated. Furthermore the disease was more frequently severe in the affected organs of the animals that had not received treatment than in the organs of the animals that had been treated.

Generally speaking, the results obtained in this experiment were in conformity with those of similar experiments reported previously. The animals in the treated group lived longer than those that were not treated and among the treated animals the disease was less severe, fewer organs were affected and when the disease was present, it was usually nonprogressive.

Specimens for biopsy: Microscopically, lesions of tuberculosis were found in the biopsy material from 8 of the 16 guinea pigs in the treated group from which specimens from the liver were obtained. Seven of the 12 specimens obtained from the livers of the animals in the control group were found to contain tuberculous lesions. We were especially interested in comparing microscopically the

FIG. 3. *a*: Discrete epithelioid tubercle in biopsy specimen of liver, forty-nine days after subcutaneous inoculation with tubercle bacilli; untreated or control group (×150); *b*: same liver as shown in *a* but as it appeared at the time of necropsy one hundred and twenty-six days after infection. Note the extensive destructive changes (×47).

FIG. 4. *a*: Tuberculous nodule in portal space; biopsy specimen obtained forty-nine days after inoculation with tubercle bacilli; control group (×47); *b*: wide-spread destructive tuberculosis in same liver as shown in *a* at the time of the animal's death one hundred and fifty-eight days after infection (×47).

FIG. 5. *a*: One of several small nodular regions of tuberculosis seen in the biopsy-specimen of liver forty-nine days after guinea pig had been inoculated with tubercle bacilli (×100); *b*: portion of same liver shown in *a* when the animal was killed after having been treated with promin for one hundred and eighty-four days. Animal was devoid of recognizable lesions of tuberculosis at necropsy (×47).

FIG. 6. *a*: One of several epithelioid tubercles found in biopsy specimen of liver obtained forty-nine days after animal had been inoculated with tubercle bacilli (×100); *b*: portion of the same liver shown in *a* after treatment for one hundred eighty-four days with promin. Tuberculosis not recognizable in the liver (×47).

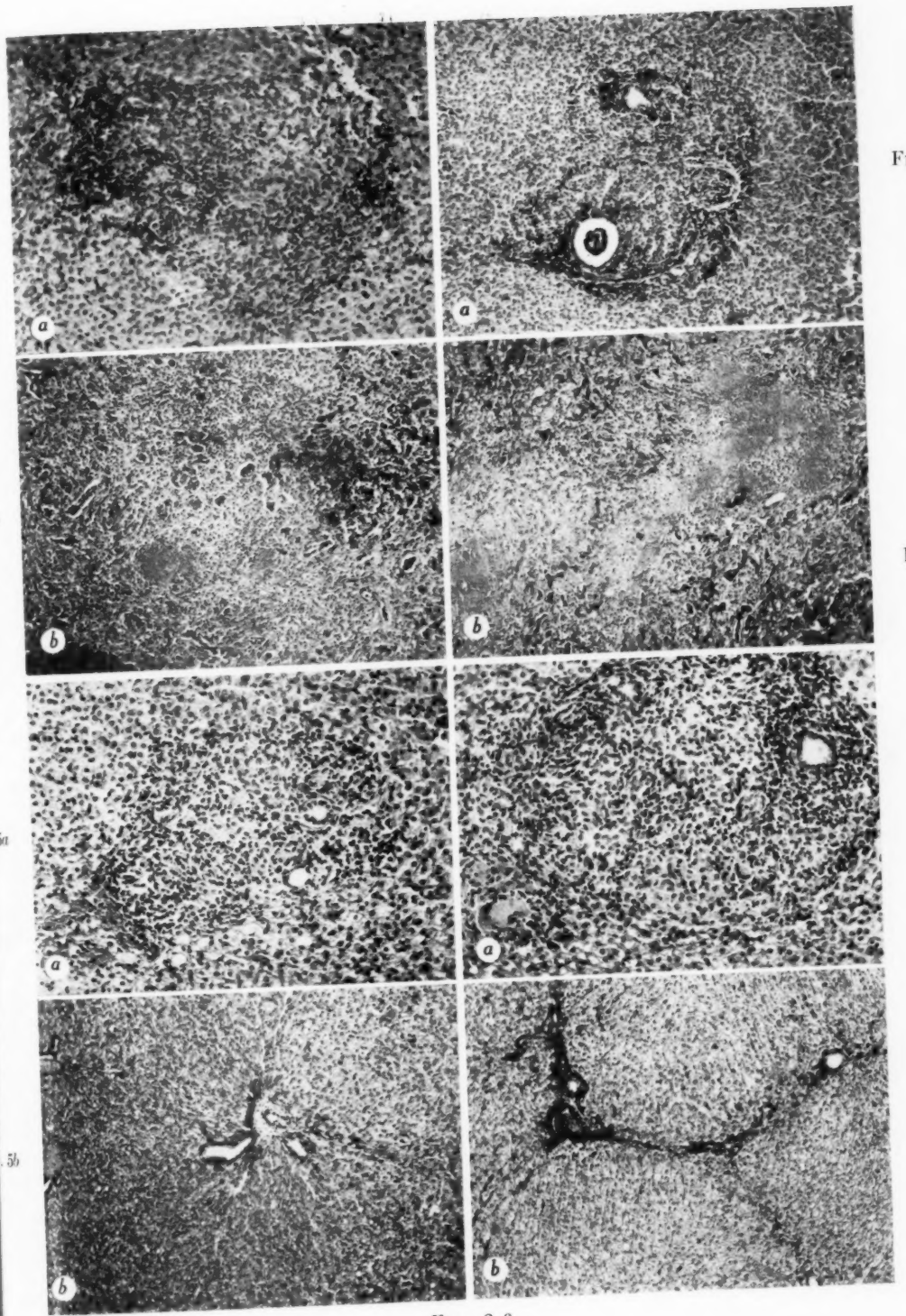


FIG. 4*a*

FIG. 4*b*

FIG. 6*a*

FIG. 6*b*

FIGS. 3–6

tissues obtained from the respective livers at biopsy with the specimens obtained months later at necropsy.

Although the animals in group 2 had been receiving promin in their feed daily for seven days before biopsy was done, there were no essential differences at the time of biopsy between the lesions from the treated and those from the control or untreated animals. The important feature of this phase of the study was that there were definitely present at the time of biopsy, in the livers of

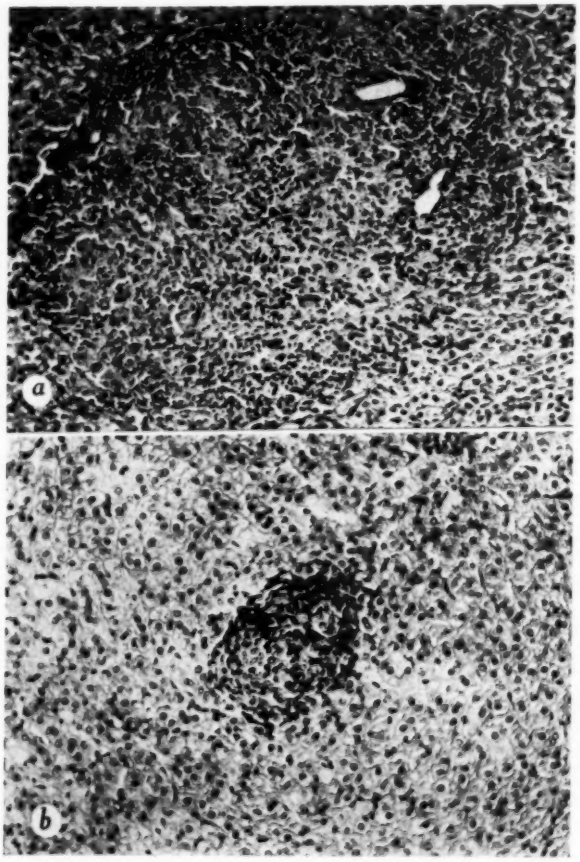


FIG. 7. *a*: One of many tuberculous nodules in biopsy specimens of liver forty-nine days after infection (×87); *b*: small atrophic nodule composed of epithelioid cells and lymphocytes in portion of same liver shown in *a* after animal had received promin daily for one hundred eighty-four days (×100).

both groups of guinea pigs, anatomical signs of a progressive, unquestionably tuberculous disease.

When the same livers were again compared microscopically several weeks to months later, striking and important differences were clearly apparent. The disease in the livers of the animals that did not receive promin had continued to progress. The lesions had become larger and more numerous and destructive with consequent replacements of much to most of the liver by the morbid

tissue (figures 3 and 4). Necrosis was observed commonly and acid-fast bacillary forms were readily demonstrable. With the exception of the one animal previously mentioned, the findings at necropsy in the livers of the treated animals were in marked contrast to those in the control group. In the livers from 4 of the 8 treated animals in which lesions had been present in the biopsy specimen, no signs of tuberculosis were seen at necropsy (figures 5 and 6).[9] In a few instances small atrophic foci of epithelioid cells and lymphocytes were found in livers from animals that had been treated (figure 7). While the structures of such foci were not sufficiently characteristic to make their tuberculous character certain, the fact that they occurred in an organ in which the presence of lesions of tuberculosis had been determined previously in a biopsy specimen provides presumptive evidence that the small foci represent the residual of a process that was established months previously.

Hepatic cultures: The results of the attempts to culture tubercle bacilli from the suspensions prepared from portions of the livers of the treated and the untreated guinea pigs revealed two facts. (*1*) With two exceptions positive cultures of acid-fast bacilli were obtained from livers in which morphological evidence of tuberculosis was present. (*2*) With one exception cultures were negative from suspensions made from livers in which lesions were not found. In the one exception only one of eight slants of medium yielded positive results. The results indicated that when lesions regressed under the influence of chemotherapy the causative agent was also likely to be diminished or eliminated during the process.

COMMENT

From the results obtained from this study we believe that it has been definitely established that a tuberculous process induced experimentally and characterized by cellular foci consisting of histiocytes, epithelioid forms and lymphocytes can be resolved under the influence of a chemotherapeutic agent of the sulfone group. Studies we have previously reported indicated that this was true but in the absence of information obtained from the same organ before and after treatment began, definite proof of what had occurred was difficult to assemble. When material obtained for biopsy from animals before treatment was judged by direct comparison with material subsequently obtained at necropsy from the same animals after a course of treatment the effect of the drug became clearly apparent. In most instances not only did the disease fail to progress under the influence of promin but instead regression and ultimately resolution took place. Although the observations at biopsy are limited to material obtained from the liver, necropsy findings in this and in experiments that were reported previously indicate that comparable results occurred in other

[9] It should be emphasized that the limitations imposed by the procedure necessary to obtain biopsy specimens precluded sections that measured more than 2 to 3 sq. mm. At necropsy the liver was fixed *in toto* and after fixation two large blocks were selected for the purpose of histological sections. The area of these sections measured several square centimeters. It is evident that the possibility for finding lesions that may have been present was greater in the material obtained at necropsy than from that obtained for biopsy.

organs and tissues that contained tuberculous lesions at the time treatment with promin began.

The failure in most instances to obtain positive cultures of acid-fast bacilli from suspensions prepared from the livers of the animals that had been treated with promin and in which lesions of tuberculosis were not found at necropsy provides a reason for suggesting that, when tuberculous lesions in a guinea pig are finally resolved after the therapeutic application of promin, the tubercle bacilli as well as the morbid changes are eliminated.

The results of this study strengthen rather than weaken confidence in the ordinary control methods of animal experimentation. The data obtained are entirely consistent with those secured in other experiments in which biopsy was not performed. However, the procedure followed in this study makes it possible to know with certainty that lesions of tuberculosis were actually present during at least the early phases of the treatment with promin. How much time was required for lesions to resolve in those animals that were without recognizable lesions when the animals were killed after receiving treatment for one hundred and eighty-four days is not known.

The results of this experiment emphasize again the consistently pathogenic behavior of the infecting organism H37RV. Not only were convincing signs of tuberculosis present at necropsy in all of the untreated guinea pigs but in addition in practically all instances the disease was present in sufficient severity to have been responsible for the animal's death. The experience gained indicates quite definitely that, had the animals in group 2 not been treated or had the treatment been less effective than that obtained with the compound used, the animals in this group in all probability would have died eventually of tuberculosis. The difference in the mortality rate and in the amount and character of the tuberculous disease present in the two groups of animals indicates that a factor was operative in the treated group that was not operative in the group that was not treated. One can only conclude that the deterrent factor was supplied by the drug that had been given with therapeutic intent.

SUMMARY AND CONCLUSIONS

A total of 51 guinea pigs was inoculated subcutaneously with tubercle bacilli, strain H37RV. At the forty-second day when all were found to be sensitized to tuberculin intracutaneously administered, the animals were divided into two groups. Group 1 consisted of 31 animals. These were not treated and were considered as controls. Group 2 consisted of 20 animals and, starting with the forty-second day, each animal in this group received daily with its feed approximately 350 to 450 mg. of sodium p,p′-diaminodiphenylsulfone-N,N′-didextrose sulfonate (promin). One week later laparotomy was performed on all the animals in group 2 and on 12 animals in group 1 in order to obtain a specimen of liver for microscopical study. Five animals died as a consequence of laparotomy, one in the control group and 4 in the group that was being treated. As a consequence of the observations at biopsy it was determined definitely that tuberculosis was present in the livers of both treated and untreated animals at the time treatment was begun. These findings were compared eventually with the findings

obtained from a study of the tissues secured at necropsy. The experiment continued until the last of the animals in the control group had died. This occurred two hundred and twenty-four days after infection. At that time only 3, or 19 per cent, of the treated animals were dead.

The results of this study confirm our previous reports that sodium p,p′-diaminodiphenylsulfone-N,N′-didextrose sulfonate (promin) is capable of exerting a definite therapeutic influence on a previously established experimental tuberculosis. The procedure followed has provided morphological evidence that in most instances tuberculous lesions present when treatment began resolved or became regressive under the influence of the therapeutic agent.

SUMARIO Y CONCLUSIONES

Un total de 51 cobayos fué inoculado subcutáneamente con bacilos tuberculosos cepa H37RV. A los cuarenta y dos días, cuando se les encontró a todos sensibilizados a la tuberculina administrada intracutáneamente, se dividió a los animales en dos grupos: el Grupo 1 constaba de 31 animales, que no fueron tratados, sino que fueron considerados como testigos. El Grupo 2 componíase de 20 animales, y, a partir del cuadragésimosegundo día, cada animal de este grupo recibió a diario con su alimentación unos 350 to 450 mg. de p,p′-diaminodifenilsulfon-N,N′-bidextrosa sulfonato de sodio (promina). A la semana se laparotomizó a todos los animales del grupo 2 y a 12 del Grupo 1, a fin de obtener un trozo de hígado para estudio microscópico. Cinco animales murieron a consecuencia de la laparotomía: uno en el grupo testigo y cuatro en el grupo en tratamiento. A consecuencia de las observaciones realizadas en la biopsia, se determinó definitivamente que había tuberculosis en los hígados de los animales tanto tratados como no tratados al iniciarse el tratamiento. Estos hallazgos fueron comparados más tarde con los obtenidos en el estudio de los tejidos tomados en la autopsia. El experimento continuó hasta que murió el último de los animales del grupo testigo, lo cual tuvo lugar a los 224 días de la infección, para cuya fecha sólo habían muerto 3, o sea 19 por ciento, de los animales tratados.

Los resultados de este estudio confirman previos informes, en el sentido de que el p,p′-diaminodifenilsulfon-N,N′ bidextrosa sulfonato de sodio (promina) es capaz de ejercer un influjo terapéutico bien definido sobre una tuberculosis experimental previamente establecida. La técnica utilizada ha aportado datos morfológicos de que en la mayor parte de los casos las lesiones tuberculosas presentes cuando comenzó el tratamiento, se resolvieron o volvieron regresivas bajo el influjo del elemento terapéutico.

REFERENCES

(1) Feldman, W. H., Hinshaw, H. C., and Moses, H. E.: The effect of promin (sodium salt of p,p′-diamino-diphenyl-sulfone-N,N′-dextrose sulfonate) on experimental tuberculosis, A preliminary report, Proc. Staff Meet., Mayo Clin., 1940, *15*, 695.

(2) Feldman, W. H., Hinshaw, H. C., and Moses, H. E.: The treatment of experimental tuberculosis with promin (sodium salt of p,p′-diamino-diphenyl-sulfone-N,N′-dextrose sulfonate), A preliminary report, Proc. Staff Meet. Mayo Clin., 1941, *16*, 187.

(3) Feldman, W. H., Hinshaw, H. C., and Moses, H. E.: Promin in experimental tuberculosis, Am. Rev. Tuberc., 1942, *45*, 303.

RESPONSE OF SCAR TISSUE TO TUBERCULIN[1]

DIRAN YEGIAN AND JOSEPH KURUNG

The formation of fibrous tissue is one of the important pathological manifestations of chronic pulmonary tuberculosis, yet a careful review of the literature fails to reveal any reference concerning the response of fibrous tissue to tuberculin. The object of the present study, therefore, was to discover whether fibrous tissue as developed in traumatic scars of the skin in tuberculous patients and animals would react to tuberculin.

In the 42 patients included in this series, the scars were on the arm in 20, on the chest in 10, and on the abdomen in the remaining 12. The scars were from one to twenty years old and varied in size from 2 x 5 cm. to 4 x 10 cm. The Vollmer tuberculin patch was applied to the scar and to the adjacent healthy skin. The tuberculin reactions were read at the end of forty-eight and seventy-two hours. Each scar in the present series reacted to tuberculin and, in some instances, the reaction was like that of the normal skin, the area of inflammation being slightly larger than that of the patch, associated with oedema and, at times, with the formation of pustules. In the majority of the scars, however, the outline of the inflammatory area was irregular and occasionally patchy. In a few patients, the total area of inflammation presented by the scar was larger than that of the adjacent healthy skin. The location and the age of the scar did not materially affect the extent of the inflammation. One would surmise that the inflammatory response of the scar would be very mild owing to the restricted capillary bed. It is possible, however, that this restriction may delay the dispersion of the tuberculin and thus account for the unexpected extent of the inflammation.

It was not possible to ascertain with any degree of accuracy in the present series of 42 patients, whether the scars were formed prior or subsequent to the development of tuberculin sensitization. Experiments were therefore conducted in guinea pigs to determine whether a surface scar, like the normal skin, responds to tuberculin shortly after the occurrence of infection, and whether sensitization can be transmitted to scar tissue.

Technique: In guinea pigs it is not possible to produce a surface scar of sufficient size for the application of tuberculin by the excision of a square inch or more of skin, because only a linear scar is left when the wound heals. The same holds true when a similar area of skin is cauterized. The procedure here described permits the formation of a sizeable surface scar. The back of the animal, proximate to the spine, is shaved and, under aseptic conditions, two transverse incisions are made through the skin and subcutaneous tissues. The incisions are one inch long, approximately two inches apart and parallel to each other. The skin lying between the incisions is then separated from the underlying tissues by blunt dissection, and a microscopical slide 1 x 3 inches is inserted

[1] From the New York State Hospital for Pulmonary Tuberculosis, Ray Brook, New York.

into the channel thus formed. The glass slide is kept in position by a string which passes beneath the glass slide and is firmly tied over the separated skin (figure 1). Each animal is placed in a separate cage with sawdust bedding, and the cages are kept scrupulously clean. These precautionary measures will prevent any untoward infection of the wound. Approximately fifteen days following the operation, the flap of skin overlying the microscopical slide is

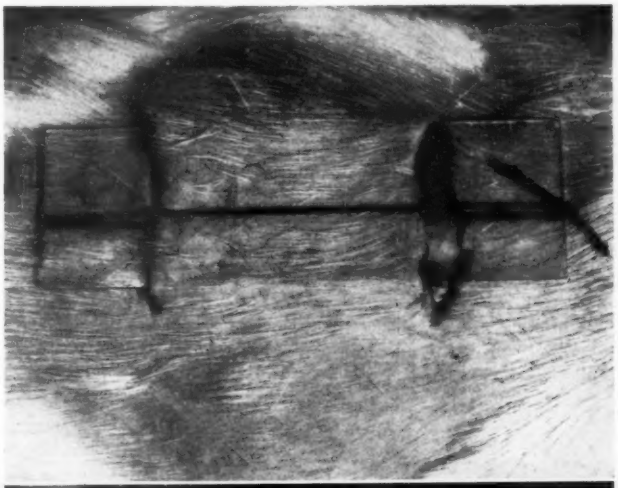


FIG. 1

FIG. 2

sloughed. The removal of the glass slide reveals that the surface of the underlying tissues is covered with fresh granulations. These granulations, at the end of six months, are converted into a mature dense scar, approximately 2 cm. square (figure 2). Cross sections of such a mature scar are about 2 mm. thick and stained microscopical preparations disclose that the scar is composed of dense fibrous tissue with a sparse vascular supply.

The first experiment comprised 15 healthy guinea pigs about one year old and

weighing approximately 500 g. By the technique above described a mature surface scar six months old was produced in each animal. Each animal, after the mature scar was formed, received an intracutaneous injection of Old Tuberculin to determine whether sensitization was present. None of the animals presented a reaction. Each animal then was given a subcutaneous injection in the groin of 50 mg. of attenuated tubercle bacilli, strain R1. Four weeks following the subcutaneous injection of tubercle bacilli, 0.1 cc. of a 5 per cent solution of Old Tuberculin was injected into the scar and into the healthy skin opposite the scar. The inflammatory response of the scar was comparable to that of the healthy skin as regards the area of inflammation, the amount of necrosis at the site of injection and the presence of oedema.

The experiment, therefore, disclosed that surface scars become sensitized to tuberculin within four weeks following infection with the tubercle bacillus, and that the inflammatory response is comparable to that of the healthy skin.

The second experiment was carried out to ascertain whether sensitization is transmitted to surface scars. The 10 guinea pigs in this group received a subcutaneous injection into the groin of 50 mg. of attenuated tubercle bacilli, strain R1. The animals in this group, after a lapse of five months reacted to an intracutaneous injection of tuberculin. At this time, a surface scar was produced in each animal in the manner already described. The mature, six-months old scar was injected with 0.1 cc. of a 5 per cent solution of Old Tuberculin, and the inflammatory response was similar to that of the healthy skin.

This experiment revealed that, in guinea pigs, sensitization is transmitted to scar tissue.

CONCLUSIONS

In tuberculous patients, the inflammatory response of scar tissue to tuberculin is comparable to that of the normal skin. The same holds true for scars produced experimentally. The experimental evidence presented, moreover, indicates that scar tissue shares in the reaction to tuberculin, at least in guinea pigs, and that sensitization can be transmitted to scar tissue. These observations are closely related to studies dealing with the pathogenesis of tuberculosis.

CONCLUSIONES

En los tuberculosos, la respuesta inflamatoria del tejido cicatricial a la tuberculina es comparable a la de la piel normal, y lo mismo reza con las cicatrices producidas experimentalmente. Además, los datos experimentales aquí presentados indican que el tejido cicatricial participa en la reacción a la tuberculina por lo menos en los cobayos, y que esta sensibilización puede ser trasmitida al tejido cicatricial. Estas observaciones se relacionan íntimamente con los estudios relativos a la patogenia de la tuberculosis.

A NEW METHOD OF STAINING TUBERCLE BACILLI[1]

EMIL WEISS

The staining of tubercle bacilli occupies an important place among the various staining methods used in microbiology. This stain seems to rank in importance next to the Gram stain. Since the publication of the original method of staining tubercle bacilli (3), many modifications have been recommended (2, 5, 6). The objective of most of these methods was the same, namely, to stain the acid-fast bacilli with a certain dye and the other organisms with a contrasting dye. Most of these procedures were not widely used, and only a few (4, 5, 6, 11) are at present in common use.

The essential requirements for a widely used method are, first, the procedure must be easily carried out; second, it must be effective; and, third, the reagents must be stable. Only a few methods answer completely these fundamentals.

Most of the methods (2) have certain properties in common: (*1*) The acid fast bacilli are stained with a contrasting dye, usually fuchsin. (*2*) Frequently heat is applied in order to facilitate better penetration of the dye in the body of the bacteria. (*3*) The decolorizing agent contains a small amount of acid in order to decolorize all other bacteria and tissue structures except the acid-fast bacilli. (*4*) For the other tissues and bacteria a different dye is employed to stain the background, usually methylene blue.

The various modifications (2) differ chiefly as to (*1*) the dye used for the staining of tubercle bacilli; (*2*) the various agents which are employed for decolorizing; (*3*) the contrasting stain for other bacteria and tissue structures; (*4*) the concentration and temperature of the dyes and reagents; and (*5*) the extent to which these procedures affect other acid-fast bacilli.

Several dyes have been recommended for the staining of tubercle bacilli (3), but fuchsin in various concentrations and in combination with other dyes and reagents is most extensively used. The great disadvantage of fuchsin is that it deteriorates rapidly. A great many decolorizing agents have been recommended for the removal of the dye from all other bacteria and tissue structures except the tubercle bacilli. The possibility that some agents may also decolorize more or less a number of tubercle bacilli prompted the introduction of a number of substitutes (2). For contrast-staining, methylene blue in various concentrations and solutions is mostly commonly used. Among the other dyes used for the same purpose the following merit special mention: vesuvin, aurantia, fluorescin, chrysoidin, malachite green, eosin, crystal violet, tropaeolin, safranin, orange G., haematoxylin, etc.

Frequently the tubercle bacilli appear in sputum as very thin rods and, if only a small number are present, there is doubt in the mind of a less experienced technician as to whether the red-stained structures are actually tubercle bacilli. On the other hand, there exists a possibility that the acid-fast bacteria in discharges from tissues are occasionally decolorized. The staining of tubercle

[1] From the Department of Pathology and Bacteriology, Chicago Eye, Ear, Nose and Throat College, Chicago, Illinois.

bacilli also depends greatly upon their chemical composition (1, 10). It has been observed by many investigators that two factors in particular disturb and complicate the interpretation of smears stained for tubercle bacilli: (*1*) the presence of sediment of the dye used for staining of tubercle bacilli and (*2*) many slender forms are easily covered up in the thicker portions of the smear and easily overlooked.

The author considered it worth while to concentrate his studies on the following factors: (*1*) To select the most suitable dye for the staining of tubercle bacilli which will remain stable. (*2*) To select an effective and durable decolorizing agent which does not affect the stained tubercle bacilli. (*3*) To select the most appropriate contrasting dye which remains stable. (*4*) To devise the entire technique in such a manner that an ordinary laboratory worker can carry it out without difficulty. (*5*) To enlarge and thicken the tubercle bacilli without deforming them. This can be accomplished by the use of a stable and effective mordant previous to the application of the staining procedure.

Some years ago in devising methods for staining of flagella, spirochetes and fungi (7, 8, 9), the author introduced a special mordant which caused the bacteria to appear thicker, larger and more deeply stained. Considering these advantages, the author considered it worth while to apply the same principle in the staining of acid-fast bacilli. The preliminary experiments indicated that all the acid-fast bacteria to which this principle was applied, appeared larger and thicker as compared to the ordinary staining method for acid-fast bacilli. It further disclosed the possibility that the danger of decolorizing the acid-fast bacilli is far less than with other methods. It remained to select the most suitable contrasting dye for the acid-fast bacilli, a sensitive decolorizing agent and the most satisfactory dye for the other bacteria and tissue structures. In order to secure the necessary information a number of experiments were performed, some of which are described below.

EXPERIMENTS

Material: (*1*) A number of sputa which contained numerous tubercle bacilli were mixed together and many smears prepared on slides. A great effort was made in all instances to prepare thin and uniformly spread smears so as to avoid the formation of thick spots on the slides which are decolorized only with the greatest difficulty.

(*2*) Smears were prepared from cultures of tubercle bacilli, human and bovine type. In addition, smears were prepared from cultures of *Mycobacterium butyricum* and *berolinense*.

(*3*) Smears from cultures of diphtheria bacilli in order to determine the effect of the proposed staining procedure on metachromatic bodies.

(*4*) Smears from discharges containing pneumococci and other capsulated microorganisms.

(*5*) Smears from cultures of spore-forming bacteria.

(*6*) Smears from young cultures of various motile bacteria.

(*7*) Smears from oral afflictions containing many spirochetes of various types.

(*8*) Smears from cultures of various nonpathogenic fungi.

All smears were stained according to the ordinary Ziehl-Neelsen method and according

to the proposed procedure. The results revealed that the tubercle bacilli stained according to the proposed method appeared considerably thicker and longer; the intensely red stained bacilli contrasted very distinctly against the blue background of other bacteria and tissue structures. Smears from cultures of tubercle bacilli, human and bovine type, stained likewise very well. Some other acid-fast bacilli, such as *Mycobacterium butyricum* and *Mycobacterium berolinense*, took the stain very well. The metachromatic bodies of diphtheria bacilli appeared considerably larger than those stained according to special procedures devised for this purpose. The diphtheria bacilli appeared likewise thicker and larger. This staining procedure did not stain the capsules which appeared only sharply outlined. The spores appeared considerably swollen causing a slight distortion of the enlarged rods. This staining procedure did not stain flagella more effectively than the special method previously recommended (7). The spirochetes appeared thicker, larger and more deeply stained than when ordinary staining methods were applied. Otherwise, this procedure offered the same favorable results as the previous special method (8). The same favorable results were obtained on fungi. The contrasting staining was very satisfactory and equally effective as on tubercle bacilli. The Ziehl-Neelsen method or any of its modifications did not offer the same advantages.

Selection of the dye for tubercle bacilli: The following dyes were tested: Ziehl's carbofuchsin, saturated watery solutions of safranin, pyronin G., neutral red, brilliant green, methyl green, methylene green, toluidine blue, gentian violet, Loeffler's methylene blue, and Delafield's haematoxylin. It was found that the saturated solutions of safranin and pyronin were preferable to carbonfuchsin because they give an equally good staining effect and keep well. Carbofuchsin or any solution of it does not keep very long. The other dyes did not offer any particular advantages.

Selection of the decolorizer: The following acids were tested in various concentrations and in combination with 95 per cent alcohol and acetone: sulfuric, nitric, hydrochloric, and acetic acid. It was found that a 15 per cent solution of glacial acetic acid in acetone gave equally good or better results than any other tested solution or concentration. An excessive decolorization with this decolorizer can be easily avoided. A subsequent thorough washing with distilled water was found advisable.

It was observed that the decolorizing agent used in ordinary methods for acid-fast bacilli was not effective on slides pretreated with the mordant. This decolorizing agent represented a much stronger solution than that used in ordinary acid-fast staining methods. If this new decolorizing agent is used in the ordinary acid-fast staining methods, it causes a complete decolorization of all acid-fast bacilli. The proposed decolorizer offers a special advantage in comparison with other agents in that it simultaneously swells the bacteria while it decolorizes them.

Selection of the contrasting dye for other bacteria and structures: The same dyes named above were tried to ascertain their usefulness as contrasting dyes. It was found that Loeffler's methylene blue was by far the most suitable contrasting dye for this purpose.

The addition of a mordant to the procedure: The composition of the mordant previously recommended for the flagella (7) and spirochetes (8) was slightly altered. It was found that this mordant caused a uniform thickening and enlargement of the bacterial bodies without producing any deformities.

THE PROPOSED PROCEDURE

As a result of the above experiments and many other observations not included in this report, the following staining procedure for tubercle bacilli has been devised:

(1) *Mordant:* It consists of two separate solutions. Solution A contains 100 g. of tannic acid dissolved in 100 cc. of 95 per cent alcohol. Solution B contains 15 cc. of glacial acetic acid diluted to 100 cc. with 15 per cent dilution of "solution formaldehyde" (Merck). Before using the mordant one part of solution A and two parts of solution B are mixed together. This mixture does not require filtering and keeps for several weeks. Solutions A and B keep indefinitely.

(2) *Safranin (or pyronin) stain:* Two and one-half g. of safranin or pyronin are dissolved in 100 cc. of 10 per cent alcohol. The dissolving process is facilitated by the application of heat. The solutions are then filtered and keep indefinitely.

(3) *Decolorizer:* Fifteen cc. of glacial acetic acid are diluted to 100 cc. with acetone. This decolorizer keeps very well.

(4) *Loeffler's methylene blue:* Thirty cc. of a saturated alcoholic solution of methylene blue (5 g. dissolved in 100 cc. of 95 per cent alcohol) are diluted with 100 cc. of a 1:10,000 solution of potassium hydroxide. The filtrate keeps well.

Staining technique: (*1*) Prepare uniformly thin smears and fix the dry smears over the flame. (*2*) Cover the slides with the above mordant-mixture and steam for five minutes. (*3*) Wash with running water. (*4*) Cover the smears with the above safranin or pyronin stain and steam for five minutes. (*5*) Wash with running warm water. (*6*) Decolorize the slides with the above decolorizer until they become colorless. (*7*) Wash vigorously with running warm water. (*8*) Cover the smears with Loeffler's methylene blue for one minute. (*9*) Wash with running water and allow the slides to dry. The tubercle bacilli appear as large, thick, deeply red stained rods while the other bacteria and tissue structures are stained blue.

Evaluation of the procedure: The proposed method has been compared with the Ziehl-Neelsen method on at least 250 diagnostic smears. The tubercle bacilli appeared not only thicker and larger but also more numerous. These observations are based on actual counts performed on the above specimens.

DISCUSSION

A new method of staining tubercle bacilli has been presented which introduces some new advantages and disposes of some disadvantages previously observed so frequently in various other procedures. The introduction of a mordant which keeps and which effectively enlarges and thickens the bacteria without deforming them offers a definite advantage. It only slightly retards the staining process. It most certainly exceeds the effect of phenol which is used in many methods in combination with fuchsin and less frequently with other dyes for the staining of tubercle bacilli (2). In addition, phenol causes a gradual deterioration of any staining solution in which it is dissolved. Frequently, a number of tubercle bacilli appear very thin and can easily be overlooked in thicker portions of the smears. No method which uses aniline dyes for the staining of tubercle bacilli enlarges the tubercle bacilli. That the slender forms can be more easily decolorized than the thicker forms is self-evident.

The great majority of staining methods for tubercle bacilli employ fuchsin in combination with phenol and less frequently in combination with other chemicals for the demonstration of tubercle bacilli (2). Fuchsin does not keep in any solution; it constantly forms a sediment which may lead to erroneous interpretation. For this reason in this procedure other dyes which remain stable have been substituted for fuchsin, such as 10 per cent alcoholic solutions of pyronin or safranin.

Among the various decolorizers, ethyl alcohol in combination with nitric acid is most frequently used. Its decolorizing power is not sufficient to produce satisfactory results in this method, so it has been replaced by a more effective decolorizer in the form of a 15 per cent solution of glacial acetic acid in acetone. The same observations were made with hydrochloric and sulfuric acids in various dilutions, alone or in combination with alcohol. Acetone has been used previously by several authors (3), while acetic acid has been used only by a few (2). There is no record that a combination of glacial acetic acid with acetone has ever been recommended for this purpose. The acetic acid-acetone mixture decolorizes and swells the bacteria simultaneously. No other reported decolorizer produces a similar effect. Picric acid has been recommended as a decolorizer by several authors (3). It decolorizes and at the same time stains the background slightly. If acids are used for decolorization there always remains the possibility that some tubercle bacilli might have been decolorized also. For this reason several authors have recommended various alkaline solutions in place of the acids (2). Not even alkaline decolorizers exclude completely the possibility that occasionally some tubercle bacilli are decolorized. The composition of the recommended decolorizer has been decided upon after the resistance of the slides, pre-treated with the mordant, has been satisfactorily determined.

The selection of a contrasting dye for the other bacteria and tissue structures did not encounter any difficulties. Loeffler's methylene blue was selected in preference to other dyes because it contrasts very effectively the pyronin and safranin. In addition it keeps very well. It also has been used to date most frequently for this purpose (2, 5, 6).

SUMMARY

A new method of staining tubercle bacilli has been devised and described. It offers the following advantages:

1. It enlarges and thickens the tubercle bacilli and other bacteria.
2. The tubercle bacilli and the other microörganisms are very effectively contrasted by the selected staining solutions.
3. The staining solutions and the reagents keep well.
4. The procedure is easily carried out.

SUMARIO

La nueva técnica aquí descrita para la coloración de los bacilos tuberculosos posee las siguientes ventajas:

1. Agranda y espesa los bacilos tuberculosos y otras bacterias.

2. Las soluciones de colorante escogidas contrastan en forma muy eficaz los bacilos tuberculosos y los otros microbios.

3. Las soluciones de coloración y los reactivos se conservan bien.

4. Es fácil de llevar a cabo.

REFERENCES

(1) Churchman, J. W.: Staining Reactions of Bacteria. The Newer Knowledge of Bacteriology and Immunity, University of Chicago Press, 1928, pp. 31–33.

(2) Ficker, M.: Methoden der Bacterienfaerbung, Handb. d. Path. Mikroorg., Gustav Fischer und Urban and Schwarzenberg, Jena, Berlin und Wien, 1929, *9/2*, pp. 747–760.

(3) Koch, R.: Die Aetiologie der Tuberkulose, Berl. klin. Wchnschr., 1882, *19*, 221.

(4) Neelsen, F.: Ein casuistischer Beitrag zur Lehre von der Tuberkulose, Fortschr. d. Med., 1885, *111*, 200.

(5) Parr, W. H., and Williams, A. W.: Pathogenic Microorganisms, Lea and Febiger, Philadelphia, 1939, pp. 126–128.

(6) Topley, W. W. C., and Wilson, G. S.: The Principles of Bacteriology and Immunity, William Wood and Company, Baltimore, 1936, pp. 288–291.

(7) Weiss, E.: Method of staining flagella, J. Infect. Dis., 1928, *43*, 228.

(8) Weiss, E.: A simple method for staining spirochetes, J. Lab. & Clin. Med., *14*, 1191.

(9) Weiss, E.: A simple method for staining fungi, Proc. Soc. Exper. Biol. & Med., 1933, *30*, 466.

(10) Wells, H. G., DeWitt, L. M., and Long, E. R.: Chemistry of Tuberculosis, Williams and Wilkins Company, Baltimore, 1923, pp. 85–104.

(11) Ziehl, F.: Zur Faerbung des Tuberkelbazillus, Deutsche med. Wchnschr., 1882, *8*, 451.

A DEVICE FOR INFECTING ANIMALS BY INHALATION[1]

J. L. BLAISDELL AND A. HAMBLETON

In certain fields of research, notably in tuberculosis, it is at times desirable to allow animals to become infected by inhaling a fine spray of a bacterial suspension. Suitable equipment is essential to avoid danger to the operator when using virulent strains. Calmette (1) describes a device in which the animal's head is enclosed in a small glass chamber to receive the spray, the chamber being closed by a rubber diaphragm which fits around the animal's neck. A disadvantage of this method is that the head of the animal, as well as the nostrils, are exposed to the infecting spray. This was avoided in the method described by Baldwin and Gardner (2), as the guinea pig is placed in a rubber tube which is constricted at one end, so that only the nose of the animal projects into the glass tube which receives the spray from the atomizer. This method is not well adapted to rabbits as their size and strength makes handling difficult. Lange (3) has described an apparatus for inhalation infection of rabbits, in which a rubber glove is drawn over the nose of the animal; the end of the middle finger of the glove is cut away and this allows the glove to be connected to the apparatus producing the spray. His apparatus is considerably more complicated than the one which is described below.

The apparatus which we have used exposes only the nose of the animal to the spray and has the following desirable features: (*1*) The chamber in which the infection is carried out, which of course should be connected to a fan giving a strong upward draft, may be closed during the infection, the operator squeezing an atomizer bulb outside the cabinet to provide the spray. (*2*) A large side tube, containing a cotton wool plug, is attached to the mask which fits over the animal's nose, so that there is no danger of damage to the animal's lungs by the air blast used in producing the spray. (*3*) After the animal has been exposed to the infecting spray and before removing its nose from the mask, provision is made for an air current to sweep out the bacterial spray remaining in the mask. This reduces the chance of bacterial spray coming in contact with the operator.

The essential feature of the method is a glass mask (figure 1), over the flared end of which is stretched a rubber diaphragm having a 25 mm. hole in the centre. The animal's nose is thoroughly wetted by a cotton swab soaked in 1 per cent tricresol and is pressed into this hole; the diaphragm adjusts itself to the animal's snout and gives a good seal. The complete equipment is illustrated in figure 2. For rabbits, the conventional rabbit box is used to hold the animal; for guinea pigs a smaller, slightly modified box, shown in figure 3, is used, and this box is fitted into a heavy wooden block so that it is less easily moved by the animal. In this box, used for guinea pigs, is a movable partition, which can be moved closer to or further from the head-end of the box, according to the length of the animal; corrugated metal strips on each side of the box allow

[1] From the Queen Alexandra Sanatorium, London, Ontario, Canada.

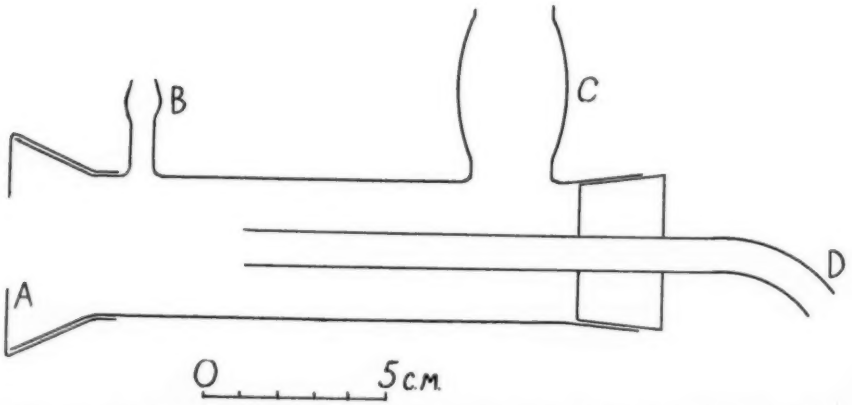


FIG. 1. Inhalation mask. A: rubber diaphragm. B: outlet tube to wash bottles and suction line. C: wide side arm, loosely plugged with cotton wool when in use. D: tube connecting to nebulizer.

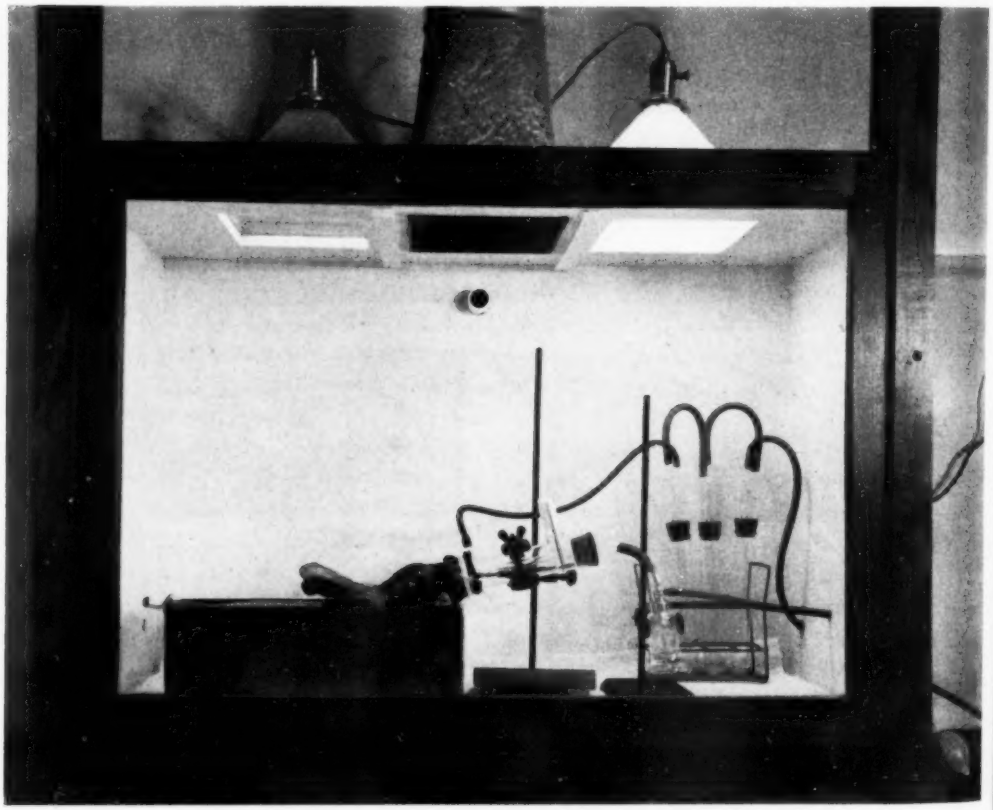


FIG. 2. Complete assembly for inhalation infection of rabbits

the partition to be adjusted to any desired place. For ease of sterilization, the animal boxes are made of sheet copper in preference to wood. The floor of the inhalation cabinet is covered by a cloth moistened with dilute phenol. Due to the friction it offers, the damp cloth minimizes the tendency of the animal boxes, and of the support holding the mask, to move if the animal struggles. The mask is of pyrex glass and can be made by any glassblower. The rubber diaphragm is made from a circle of sheet rubber about 15 cm. diameter and 1.3 mm. thick, cut from the inner tube of a motor cycle tire. After cutting the 25 mm. hole in the centre of this sheet, the rim of the flared end of the mask is smeared thinly with cement,[2] and placed on the top of the cleaned rubber sheet which lies flat on the table. Next day, when the cement has hardened, radial slits are cut from the edge of the rubber sheet to the rim of the mask; the rubber strips thus formed are folded back and tightly bound to the glass with string.

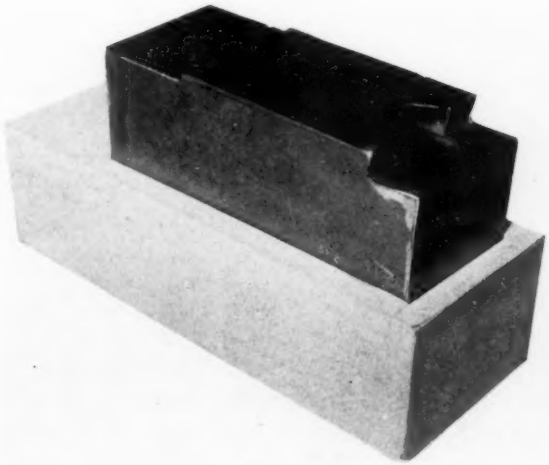


FIG. 3. Box used to hold guinea pigs, inside dimensions, 20 x 8 x 8 cm. Hole for neck, 33 mm. wide, 35 mm. long.

The cabinet in which we have used this apparatus is 90 cm. long, 41 cm. deep and 61 cm. high, inside dimensions, with sliding glass door at the front. Two glass windows built into the roof of the cabinet allow illumination from lamps placed outside. The exhaust system which ventilates the autopsy room was used to provide a strong upward draught through the cabinet. When assembled for use, the small outlet tube, B, of the mask is attached by rubber tubing to three wash bottles or tubes containing 5 per cent phenol and these in turn to a suction line which can be turned on or off as desired. During the infection, the suction line is shut off. Before removing the animal's nose from the mask the suction line is opened, thus sweeping a current of air through the mask. The wash bottles prevent bacteria from being carried to the suction pump.

[2] "Sealit" cement, Fisher Scientific Co., Pittsburgh, was used.

The bacterial spray is produced by a De Vilbiss No. 48 nebulizer[3] and is carried into the mask by means of a bent glass tube. From a rubber bulb outside the cabinet, a short heavy-walled tube runs through a hole in the wall of the cabinet to the nebulizer, to supply the air blast. The mask is adjusted to a convenient height and slope and is held in place by the usual iron clamp and stand used in chemical laboratories. A heavy weight is placed on the base of the stand, so that it remains unmoved if the animal attempts to struggle. The animal box is moved towards the mask until the animal's nose is pressed tightly into the flared end of the mask and, on finding that this is rigid and cannot be moved, the animal soon becomes quiet. A weight may be placed on the animal box if it tends to move, but we have not found it necessary. A cloth thrown over the animal's eyes encourages it to remain quiet.

With the above equipment we have inoculated approximately 100 guinea pigs and 80 rabbits. The mask described can be used for both guinea pigs and rabbits. For most of our work, using virulent strains of tubercle bacilli, we use a suspension showing 5 bacilli per oil immersion field, when 0.1 cc. of suspension is spread over an area 25 mm. square on a slide, using precautions described by Vogt, Zappasodi and Long (4); this corresponds to 1,600,000 bacilli per cc. with the microscope employed. Five puffs from the atomizer are given, and after allowing the animal to breathe the vapor for thirty seconds, the vapor is swept out of the tube by a current of air for thirty seconds. Then removing the animal from the box, its nose is again swabbed with dilute cresol.

SUMMARY

The essential feature is a glass tube, 3.8 cm. in diameter and 17.5 cm. long, which is flared at one end; over this end is a rubber diaphragm, in the centre of which is a hole 2.5 cm. in diameter. The animal, rabbit or guinea pig, is placed in an animal box and its snout, wet with disinfectant, is pressed into the hole in the rubber diaphragm, which forms a seal to minimize escape of the bacterial spray. A side arm of the glass tube, plugged with cotton wool, prevents excessive air pressure as the spray is blown in from a De Vilbiss No. 48 nebulizer. Another side arm allows an air current to sweep the residual spray out of the tube, through wash bottles of disinfectant, on completing the experiment. While infecting animals, the cabinet containing the equipment may be completely closed. The cabinet should have good upward draft.

SUMARIO

La característica esencial de este aparato es un tubo de vidrio de 3.8 cm. de diámetro y 17.5 cm. de largo, ensanchado en un extremo, sobre el cual va un diafragma de goma en cuyo centro hay un agujero de 2.5 cm. de diámetro. Colócase el animal, conejo o cobayo, en una caja *ad hoc*, y se le comprime el hocico humedecido con desinfectante, contra el agujero del diafragma, el cual forma una cápsula que aminora el escape de pulverización bacteriana. Un brazo lateral del tubo de vidrio, tapado con lana de algodón, impide toda presión

[3] The De Vilbiss Co., Toledo, Ohio.

aérea excesiva al soplarse la pulverización con un nebulizador de De Bilbiss No. 48. Otro brazo lateral permite que al completar el experimento una corriente de aire lance el resto de la pulverización fuera del tubo a botellas lavadas de desinfectante. Mientras se infecta a los animales, el gabinete que contiene la instalación puede permanecer absolutamente cerrado. El gabinete debe contar con buena ventilación hacia arriba.

REFERENCES

(1) CALMETTE, A.: Tubercle Bacillus Infection and Tuberculosis in Man and Animals, Baltimore, 1923, Williams & Wilkins Co., p. 148.

(2) (a) BALDWIN, E. R., AND GARDNER, L. U.: Reinfection in tuberculosis, Am. Rev. Tuberc., 1921, *5*, 429.

(b) BALDWIN, E. R., PETROFF, S. A., AND GARDNER, L. U.: Tuberculosis; Bacteriology, Pathology and Laboratory Diagnosis, Philadelphia, 1927, Lea & Febiger, p. 71.

(3) LANGE, L.: Behelfsmässige Vorrichtung zu Einatmungsversuchen an Kaninchen, Zentralbl. f. Bakt., (Abt. 1), 1934, *131*, 399.

(4) VOGT, A. B., ZAPPOSODI, P., AND LONG, E. R.: Bacillary counts in sputum, Am. Rev. Tuberc., 1940, *41*, 481.

STATISTICAL DATA

Edited by MARY DEMPSEY

DEATH RATES FROM TUBERCULOSIS AND DIABETES MELLITUS—1925 AND 1940

In 1925 the death rate from tuberculosis, all forms, was 86.7 per 100,000 population in the United States Death Registration Area;[1] by 1940 this death rate had fallen to 45.9 per 100,000 enumerated population for the entire continental United States. In other words, the death rate from tuberculosis was almost cut in two in fifteen years, the decline being 47 per cent.

On the other hand, the diabetes death rate increased during the same period from 16.9 per 100,000 in 1925 to 26.6 in 1940. This advance is of great interest when we consider that insulin as a means of treating diabetes, discovered in 1922, had not yet come into general use by 1925. Fifteen years later one would have expected that the more or less general adoption of the insulin treatment—in urban communities, at least—had resulted in a definite reduction in the diabetes death rate. On the contrary, the rate had increased 57.4 per cent during the fifteen-year period.

What has happened during the same interval to those persons who have both tuberculosis and diabetes? The U. S. Census Bureau publishes data on contributory causes of death only at relatively rare intervals, but such data are available for 1925 and 1940. The Bureau's findings indicate that the death rate from coexistent tuberculosis and diabetes increased slightly from 1925 to 1940; the advance was confined to persons whose tuberculosis affected the respiratory system. Because of the pronounced decline in the tuberculosis death rate from 1925 to 1940 the proportion of tuberculosis deaths in which diabetes was listed as a complication had risen from 0.60 per cent of all tuberculosis deaths in 1925 to 1.32 per cent in 1940. (Whenever a death certificate lists as causes of death both tuberculosis and diabetes, rules governing the classification of joint causes always charge the death to tuberculosis as a primary cause with diabetes as a secondary cause.)

Table 1 shows for 1925 and 1940 the number of deaths and the death rates from tuberculosis with diabetes mellitus as a contributory cause.

AGE OF TUBERCULOUS PATIENTS BY STAGE OF DISEASE

Last year certain studies were made by the Committee on Coexistent Syphilis and Tuberculosis of the American Trudeau Society working in coöperation with a committee of syphilologists appointed by the U. S. Public Health Service. In the course of these investigations it was discovered that the percentage of positive blood tests for syphilis is low in minimal cases of tuberculosis, higher among the moderately advanced cases and still higher in the far advanced group.

[1] In 1925 the Death Registration Area comprised 89.6 per cent of the population of continental United States; in 1940 the entire population of the United States was included in the Death Registration Area.

Following an interesting lead[2] presented by Dr. Henry Stuart Willis and confirmed by Dr. H. I. Spector, carefully prepared questionnaires were sent out by the American Trudeau Society to approximately 150 large sanatoria. Preliminary tabulations of data from 60 institutions scattered over 24 states confirmed the Willis and Spector figures, as shown in the following summary:

Stage of Tuberculosis	*Per Cent Positive Blood Tests for Syphilis*
Minimal	1.7
Moderately advanced	2.9
Far advanced	5.4

TABLE 1

Deaths from tuberculosis, with diabetes mellitus as a secondary cause, United States,** 1925 and 1940*

CAUSE OF DEATH AND YEAR	TOTAL DEATHS FROM TUBERCULOSIS*		DEATHS FROM TUBERCULOSIS WITH DIABETES MELLITUS AS SECONDARY CAUSE		
	Number	Death rate per 100,000 population	Number	Death rate per 100,000 population	Per cent of all tuberculosis deaths
Tuberculosis, all forms—1940	60,428	45.9	795	0.60	1.32
Tuberculosis of the respiratory system	55,576	42.2	770	0.58	1.39
Tuberculosis, other forms	4,852	3.7	25	0.02	0.52
Tuberculosis, all forms—1925	89,268	86.7	537	0.52	0.60
Tuberculosis of the respiratory system	78,103	75.9	507	0.49	0.65
Tuberculosis, other forms	11,165	10.8	30	0.03	0.27

* Whenever a death certificate lists as causes of death both tuberculosis and diabetes, rules governing the classification of joint causes always charge the death to tuberculosis as a primary cause with diabetes as a secondary cause.

** Death rates for 1940 are based on the *enumerated* population for continental United States as of April 1, 1940. Death rates for 1925 are based on the estimated population as of July 1, 1925 for the U. S. Death Registration Area, which then included 89.6 per cent of the population in continental United States.

At this point many questions presented themselves; among them were inquiries as to the median age of patients diagnosed in each stage of tuberculosis. Among members of the Committee the general impression prevailed that far advanced patients were older, generally speaking, than those with moderately advanced tuberculosis, and the latter were older than the minimal group. In other words, some authorities argued that possibly more syphilis was found among far advanced tuberculous patients for the reason that they as a group were considerably older and thus had been exposed to risk over a longer period.

It was indeed surprising to learn that very little information has ever been

[2] Transactions, National Tuberculosis Association, 1941, p. 158.

assembled showing stage of tuberculous disease by age of patient. Not only are such data of primary interest to the Committee on Coexistent Syphilis and Tuberculosis, but they are urgently needed for the intelligent planning and evaluation of several phases of our tuberculosis program.

What could affect our case-finding activities and our health education program more directly than the possible finding that patients with far advanced tuberculosis proved to be ten years older—or even five years older—than those in the minimal stage? What a direct influence such information would bring to bear on rehabilitation plans just getting well under way!

In an effort to meet this lack insofar as possible, data already at hand for 6,906 adult tuberculous patients discharged alive in 1933 from 75 public sanatoria in the United States were tabulated to show age of males and females upon admission (or readmission) to sanatoria and stage of disease at that time. Surprisingly enough, the difference in age of patients by stage of disease is much less pronounced than might have been expected. The findings are as follows:

STAGE OF TUBERCULOSIS	MEDIAN AGE OF PATIENTS UPON ADMISSION* TO SANATORIA		
	Both sexes	Male	Female
All stages	29	32	27
Minimal	28	31	26
Moderately advanced	29	32	27
Far advanced	30	32	28

* Includes readmitted patients.

Although these findings are based on a fairly large number of patients, the results must be considered inconclusive until corroborated by similar analysis of less restricted groups. For example, the 6,906 patients studied included only those sixteen years and over upon admission to the sanatorium; obviously, this restriction affects the median age. In addition, only patients with pulmonary tuberculosis of the reinfection type who left the sanatoria *alive* in 1933, after a stay of one month, were included among the group considered.

In spite of their limitations the data possess certain historical significance, inasmuch as all the patients included were discharged alive nine years ago. Since 89 per cent of them had been in the sanatoria less than two years, it is evident that most of them were admitted (or readmitted) during the years 1931–1933. Further study of age of patients by stage of disease a decade later would tend to confirm or refute these findings, provided of course that the analyses were restricted in the same way.

It is hoped that some large sanatoria, with adequate record systems, will be interested in assembling data for recent years showing the age of their patients by stage of disease. This information would possess special comparative value if restricted to adult patients (sixteen years and over) with pulmonary tuberculosis of the reinfection type.

AMERICAN TRUDEAU SOCIETY

Report of the Committee on Industrial Tuberculosis[1]

Dr. Leopold Brahdy, Chairman
Dr. Raymond C. McKay — Dr. Arthur Vorwald
Dr. Everett K. Geer — Dr. H. E. Hilleboe

This report is limited to tuberculosis among employees of hospitals (including institutions for tuberculosis). With this limitation the problem becomes simpler; many industrial hazards need not be considered, for example, those in the dusty trades. Among hospital personnel the hazard of contact with tubercle bacilli is the essential occupational problem. The report consists of three parts:

Part I: Routine examinations of employees.
Part II: When is tuberculosis in hospital personnel due to occupational contact?
Part III: A proposed epidemiologic investigation.

PART I. ROUTINE EXAMINATION OF EMPLOYEES

The great value of early case-finding for the individual employee in decreasing the length of illness and increasing the chances of complete recovery is self-evident. In some occupations early case-finding is imperative in the interest of the people served by the employees. This applies particularly to the personnel of general hospitals, since they must come in immediate and repeated contact with patients. It is unfortunate if a person is admitted for a nontuberculous disease, recovers, and is then discharged with a latent tuberculosis infection acquired during his hospital stay from an employee.

Preëmployment case-finding is financially important to all hospitals that assure sick pay or compensation for employees. The preëmployment discovery of an active lesion in an applicant means that hospitals will avoid paying compensation or sick allowance to that individual when such payment would not be properly chargeable to the institution. Several hospitals now carry the financial burden of compensation for tuberculosis which existed prior to employment because these hospitals formerly required no preëmployment examinations. Periodic examinations are also important to the hospital. Some employees will first develop demonstrable lesions in the course of employment. The hospital will pay sickness allowance or compensation and death benefits to these employees. If, by periodic examinations, these lesions are discovered in the early stages, then the hospital, as well as the patient, profits by the shorter duration of the disease and the lower mortality.

This report does not include a discussion of methods of preventing infection by contact in hospitals. It is desired, however, to note one essential procedure to determine the efficacy of the methods in use and to constantly check on

[1] This is the first in a series of reports made by the Chairman of the various American Trudeau Society Committees to the Council at the Society's annual meeting in Philadelphia, May 6–9, 1942.

whether they are being properly carried out. Among student nurses and other employees, there will be a number who are tuberculin negative before employment. The periodic tuberculin testing of these individuals will give the specific infection rate for various groups. This periodic testing serves the triple purpose of (*1*) early case-finding; (*2*) decreasing periodic roentgen examinations; and (*3*) providing a sensitive index of where and when infections are occurring.

Preëmployment examinations: This Committee recommends the following addition to the usual physical examination of *all* applicants for hospital employment:

1: A history recorded with specific reference to previous tuberculosis contact.
2: Mantoux test with standardized tuberculin properly applied and interpreted.
3: A chest roentgen examination satisfactory to a critical expert.

Protection of the hospital from later unwarranted insurance claims will be increased the more exacting the roentgen examinations are of the tuberculin-positive applicants. Additional examinations are therefore suggested, such as lateral or stereoscopic views or fluoroscopy with spot films.

Periodic examinations during employment: According to the results of the preëmployment examinations applicants should be divided into three groups for which the recommendations for subsequent periodic examinations differ.

Group A: Those tuberculin-negative on employment.

Tuberculin test should be repeated every three months (additional tests may be desirable before and after work entailing special hazard).

Those who become tuberculin-positive while employed should be kept under careful clinical observation for at least two years with repeated chest roentgen examinations; they may be then transferred to group B.

Group B: Those tuberculin-positive on employment but no history or roentgen evidence of significant tuberculosis.

Roentgen examination should be repeated at least once a year.

Group C: Those with recorded history of past tuberculosis or evidence of arrested tuberculosis on employment.

Examinations should be made in accordance with the history and findings.

PART II. WHEN IS TUBERCULOSIS IN HOSPITAL PERSONNEL DUE TO OCCUPATIONAL CONTACT?

The reply will be different for each of the three groups into which applicants for employment may be divided according to preëmployment examinations.

Group A: This group is composed of employees whose preëmployment tuberculin tests were negative and whose chest roentgenograms showed no significant lesion.

Assuming their work brought them in contact with tuberculosis and that they develop a tuberculous lesion in the course of the work, it is reasonable to assume that *the disease is due to occupational contact* (with the exceptions listed below).

Exceptions:

1: Known contact outside of employment.

An employee may have known intimate contact with open tuberculosis in his own home or social environment. This must be given consideration.

2: Contact outside of employment which is not traced.

A small percentage of negative reactors turn positive annually and the responsible contact is never traced. In any *individual* case of tuberculosis in a hospital employee, however, the probabilities are greater that a proven hospital contact, rather than such casual contact, is responsible.

3: Recent infection, but still in the tuberculin-negative period.

An applicant may have acquired the infection just prior to his preëmployment examination. The time since infection being too short for skin sensitivity to have developed, the tuberculin reaction is negative. Such applicants are therefore erroneously placed in group A.

Note: Though untraced outside contact may be significant in some communities, the sum of all these possible exceptions is small. The effect of all these exceptions is to place the individuals within this group A, in which, if lesions develop, the disease will be classified as probably occupational. In adjudicating occupational disease claims these exceptions therefore do no injustice to the individual for the effect is classification of a doubtful case in the group in which all are considered probably occupational cases.

Group B: This group is composed of employees whose preëmployment tuberculin tests were positive and whose chest roentgenograms show no significant lesion.

It may be assumed that some among the tuberculin-positive group will develop active lesions from the preëmployment infection without any relation to an occupational contact with tuberculosis. The question remains: what part does this preëmployment infection play in producing disease and what part does the occupational contact with tuberculosis play in this group? Certainly, in no individual with a positive preëmployment tuberculin reaction can it be stated categorically that he probably developed his disease because of the occupational contact, as can be asserted of those in group A.

Some clinicians believe that, from the point of view of the epidemiology of tuberculosis, there is no evidence that occupational contact with tuberculosis may cause a first-infection-type tuberculosis to develop into active disease. They believe that this tuberculin-positive group is not subject to any hazard from new contact with tuberculosis although they are subject to the hazard of active disease from the infection previously acquired. Others believe that, on the contrary, a tuberculin positive individual may develop disease because of *new* contact, or that at least he would have been less likely to develop disease if he had had no contact subsequent to the one which produced the tuberculin reaction. No single study so far published is conclusive. Because the data given by different authorities are not comparable, cumulative evidence is lacking. The members of this Committee believe that no purpose will be served by presentation of their own views.

This problem transcends the question of tuberculosis in hospital personnel. It is fundamental to all tuberculosis epidemiology and control and the solution

must be actively sought. This Committee believes the problem can be solved and later in this report proposes a method.

Group C: This group is composed of employees who have a record of clinical tuberculosis in the past or whose preëmployment X-ray films showed an apparently healed lesion.

It is clear that this group will have a considerable number of relapses under any circumstances, as has been shown by follow-up studies of patients discharged from sanatoria who have recurrences although not employed at any work that could possibly be hazardous.

Since their founding, sanatoria have employed persons in this category with careful clinical supervision. These sanatoria have been havens of employment for many, a stepping stone to return to normal occupation, and for a few the beginning of a life of service in the field of tuberculosis. Many of the ex-patients have led active lives and some even strenuous lives after the first years of hospital or sanatorium employment.

The question for this group C is: Is hospital employment hazardous in the sense that exposure to open cases may aggravate or activate apparently healed tuberculosis lesions? The fact that such persons have been employed under medical supervision in sanatoria in the past half century means that sanatorium clinicians do not believe such exposure to be hazardous for such employees. The final answer must be based on knowledge of whether such persons had recurrences in the same proportion as those in employment without contact with open tuberculosis.

Sufficient clinical experience has accumulated to indicate that the incidence of recurrence among such employees in hospitals is not greater than in other employments. There may be occupational factors other than exposure to tubercle bacilli, but there is no evidence that relapses are due to such exposure alone.

Although this conclusion is well established on a clinical basis, it should be further tested by studies similar to those hereafter proposed.

PART III. A COMPARATIVE EPIDEMIOLOGIC INVESTIGATION

This Committee proposes a coöperative study on the relative importance of endogenous and exogenous infection among hospital employees with preëmployment positive tuberculin reactions and negative chest roentgenograms. The important aspect of this proposal is that the data which are needed from hospitals have been accumulated and are being augmented each year for the practical purpose of properly administering the hospitals.

The Committee suggests that the American Trudeau Society and the National Tuberculosis Association in coöperation with the U. S. Public Health Service interest in this study a number of hospitals where careful records have been kept over a period of years. Only those hospitals would be included which met certain standards regarding repeated examinations of hospital employees and which had available complete case histories of all employees to be included in this study. Similar data for nonhospital groups with no known

exposure to tuberculosis are desirable; colleges and industries with small turnover suggest themselves for these control groups. A coördinating committee is required which will coördinate the individual studies so that the same information would be obtained from all hospital records and records of other groups so that rates of breakdown from tuberculosis could be determined in all studies by the same modified life table methods of analysis. This would make possible the valid comparison of the individual studies made by each investigator in each hospital or other group and also the collation of all the data by the coördinating committee for cumulative results.

Such studies could form the basis for a symposium at one of our future annual meetings, in which the individual workers could present their own studies, uniformly set up and similarly analyzed, and a member of the coördinating committee could summarize the experience of the group as a whole.

Only by such a definite plan with a clear-cut objective and carefully executed methods would it be possible to quantitatively measure the risk of developing tuberculosis among employees in relation to their previous infection and their contact with tuberculosis during hospital employment.

RÉSUMÉ OF REPORT ON TUBERCULOSIS AMONG HOSPITAL EMPLOYEES

For years many hospitals have required preëmployment and periodic chest examinations of their employees for the protection of these employees, for the protection of the hospital and (in general hospitals) for the protection of the nontuberculous patients. Records of these examinations are being augmented every year; they are necessary for routine hospital administration.

The Committee reports on the question, "*Under what conditions is tuberculosis in hospital employees a disease due to occupation?*" The report differs in each of three groups into which employees are divided according to preëmployment examinations.

(*1*) In an employee who was tuberculin-negative at the time of beginning employment and who develops tuberculosis in the course of work,—the disease is probably due to occupational contact.

(*2*) In an employee who has an arrested lesion which, in the course of his employment, again becomes active,—this reactivation is not due to any occupational exposure to tuberculosis.

(*3*) In an employee who was tuberculin-positive on beginning employment but had no demonstrable lesion and who develops tuberculosis in the course of work,—the evidence is inconclusive and this Committee is unable to answer the question on this third group.

An answer for the third group is important not only for hospital administrators but for all tuberculosis control. The Committee suggests a plan which may lead to the answer. It is suggested that this Society and the National Tuberculosis Association in coöperation with the U. S. Public Health Service endeavor to interest hospitals where careful records have been kept over a period of years in a coöperative study of the problem of the risk of tuberculosis among hospital personnel. Only those hospitals would be included which met certain

standards regarding clinical examinations of their employees and kept complete records.

Groups of adults not exposed to tuberculosis (nonhospital groups such as college students or industries with small labor turnover) must be included in the study as controls. If all the records of various groups which have already been made were reported in standardized form together with some further investigations, it is likely that a collation of all the information would yield a definite answer to the problem of the risk of developing tuberculosis in relation to previous infection and subsequent contact with tubercle bacilli.

WORKMEN'S COMPENSATION FOR TUBERCULOSIS

Time did not permit the Committee as a whole to consider the "status of compensation in tuberculosis in the different states." Nor is it essential that the full committee consider this because it is a matter of compilation rather than of professional judgment. For that reason the Chairman, acting as a subcommittee of one, presents the following report which is based on data in an article entitled *Occupational and Compensable Disease* by L. Brahdy in the April, 1942 number of Industrial Medicine.

The development of occupational medicine and the extension of workmen's compensation laws have brought occupational disease problems before most physicians. When meeting medical problems with compensation aspects, physicians often ask: What does the law say? They are surprised to learn that the law answers no medical questions. We shall more effectively advance occupational health and the administration of workmen's compensation if we are acquainted with certain phases of the law and with terms used in adjudication of compensation claims for injuries and occupational diseases. We should be able to distinguish between the medical aspects, which are the physician's concern and the legal administrative aspects of a problem. The latter are outside of the physician's province. He may, of course, suggest changes in the law or in the procedure where health matters are involved.

There are federal compensation laws which cover employees in the District of Columbia, harbor workers and employees of the United States Government. With the exception of Mississippi, all our states and territories have compensation laws, but no two of these laws are identical. Legal information on individual cases must be sought in the specific law of each state or territory.

Some general principles may become apparent if we group these laws according to similarities and differences. All these laws provide some medical care and sick-pay during the period of disability. The employer may pay compensation directly or may be required to pay a premium to an insurance company which will then pay the compensation and medical costs. In most states the insurance rates are government controlled. They may vary with the hazards of each industry. Where 90 per cent of the employees are clerks, the premiums are low because injuries are rare. Where the employees are house wreckers, among whom injuries are frequent and severe, the insurance premium may be

equivalent to more than half the amount of wages paid. The amount of compensation payments, or of the premiums, is added to the price of the employer's product or service like any other business expense.

In no place are all workers within the scope of a compensation law. Most states exclude farm labor and domestic help. Some states include only specified industries. In many states the employer is not required to pay compensation unless he has a certain minimum number of employees. This minimum varies from two in Oklahoma to sixteen in Alabama. In some states the minimum number clause does not apply to hazardous employments. In many states the law is not compulsory but its applicability is elective by the employer and the employee.

When we say that an injury is occupational we mean that it is the result of an accident which arose out of and in the course of employment. An employee may meet with an accident but his employment may not be covered by the compensation law of his state. In such a case, even though the injury is occupational, he is not entitled to compensation. Whether an injury is occupational is a question of fact. That fact is contained in the answer to the following question: This employee met with such and such an accident while at work; is it probable that his injury resulted from that accident? Often the answer is self-evident, sometimes it is difficult. The question is always a *medical* one. A physician will give the same answer to that same question whether it is asked in Alaska or in Florida. Let us assume the answer is: Yes, this is occupational. That answers the medical question and, then, the next question must be considered: Is the employee to be paid compensation by his employer for wages lost because of this? That question is usually phrased more briefly: Is this compensable? Whether it is compensable depends on whether it comes within the law of the state or territory that has jurisdiction. This is a *legal* question. The answer varies in different jurisdictions. When physicians differentiate between two terms, "occupational" and "compensable," they recognize a boundary separating their medical field from the legal-administrative field. Physicians—and only physicians—can decide whether a disease is occupational. Lawyers and administrators, but never physicians, must decide if an occupational disease is compensable according to the law of that state.

All compensation laws cover injuries and such diseases as are proximately caused by the injury. In any jurisdiction, if a physician testified that a compensable injury caused tuberculosis and the authorities are satisfied that his testimony is correct, then the patient is paid compensation for wages lost because of the tuberculosis. A latent tuberculosis which is aggravated by an injury so as to disable the employee is compensable as part of the injury. The employee is paid because the disease is a result of the injury, just as he is paid for an abscess developing at the site of a severe contusion. Physicians do not classify such a case of tuberculosis as an occupational disease and neither does any law. It is part of the compensable occupational *injury* and is therefore compensable.

STATES IN WHICH ONLY INJURIES ARE COMPENSABLE

Many states have included only injuries among compensable conditions. They specifically exclude occupational diseases from the compensation law. The South Dakota Compensation Act reads: "Injury shall mean only injury by accident and shall not include a disease in any form, except as it shall result from the injury." The Wyoming Law reads: "Injury shall not include a disease except as it shall directly result from an injury received in employment."

The Compensation Laws of twenty-two states and of Alaska contain a substantially similar clause. In these states tuberculosis is compensable only when it results from a compensable injury; they are:

Alabama	Maine	South Carolina
Arizona	Montana	South Dakota
Colorado	Nevada	Tennessee
Florida	New Hampshire	Texas
Georgia	New Mexico	Vermont
Iowa	Oklahoma	Virginia
Kansas	Oregon	Wyoming
Louisiana		

States with a Schedule of Compensable Occupational Diseases

Arkansas	Michigan	Pennsylvania
Idaho	Minnesota	Rhode Island
Delaware	Nebraska	Utah
Kentucky	New Jersey	Washington
Maryland	North Carolina	Also Puerto Rico

The laws of these states contain a limited list (usually called a schedule) of occupational diseases for which compensation must be paid if they disable the employee. The Rhode Island schedule contains the name of thirty-one diseases; Kentucky lists only the inhalation of noxious fumes and gases. The other states are intermediate. In none of these lists or schedules is tuberculosis mentioned. Therefore, tuberculosis acquired by a medical attendant because of contact with a patient is not compensable in any of these states. If tuberculosis is a complication of any of the scheduled (that is, compensable) occupational diseases, and if it is proximately caused by that scheduled disease, then compensation must be paid for tuberculosis. This is analogous to compensation for tuberculosis caused by a compensable injury.

STATES IN WHICH ALL OCCUPATIONAL DISEASES ARE COMPENSABLE

California	Missouri	Ohio
Illinois	New York	Wisconsin
Indiana	North Dakota	

These states have "blanket coverage" for occupational diseases. The Federal, Hawaiian and the Philippine Compensation Laws also have blanket coverage. This means that in addition to occupational injuries all occupational diseases are compensable under these laws. It is of interest to note that the

major part of our industrial population is within these jurisdictions. Connecticut, which is usually classed as having "blanket coverage," and Massachusetts will be discussed later.

In these jurisdictions the decision as to whether the disease is compensable is based on the answer to the medical question: "Did this disease originate in this patient's occupation?" In these eight states, occupational tuberculosis in a hospital employee is compensable. The following are the clauses in state laws which make the term "*compensable* occupational diseases" include *all* occupational diseases.

1. *California:* A compensable disease is "any disease arising out of employment."

2. *Illinois:* "Occupational disease" means a disease arising out of and in the course of employment. Ordinary diseases of life to which the general public is exposed outside of the employment shall not be compensable, except where the said disease follows as an incident of an occupational disease as defined in this section.
"A disease shall be deemed to arise out of the employment only if there is apparent to the rational mind upon consideration of all the circumstances, a direct causal connection between the conditions under which the work is performed and the occupational disease, and which can be fairly traced to the employment as the proximate cause, and which does not come from a hazard to which workmen would have been equally exposed outside of the employment. The disease must be incidental to the character of the business and not independent of the relation of employer and employee. The disease need not to have been foreseen or expected, but after its contraction it must appear to have had its origin in a risk connected with the employment and to have flowed from that source as a rational consequence."

3. *Indiana:* The occupational disease provisions are practically identical with those of Illinois.

4. *Missouri:* The compensation law is in two distinct parts—one for injuries and the other is elective and includes all occupational diseases. None of the large hospitals have elected to carry compensation for occupational diseases and there has been no tuberculosis claim by a hospital employee.

5. *New York:* Compensation is to be paid for "any and all occupational diseases" arising out of and in the course of "any and all employments" covered by this act.

6. *North Dakota:* "The term 'injury' includes in addition to any injury by accident, any disease approximately caused by the employment."

7. *Ohio:*	Compensation is to be paid for all occupational diseases, and the definition is given: "A disease peculiar to a particular industrial process, trade, or occupation and to which an employee is not ordinarily subjected or exposed outside of or away from his employment."
8. *Wisconsin:*	"Injury is mental or physical harm to any employee caused by accident or disease." It is compensable "where the accident or disease causing injury arises out of his employment."
9. *Territory of Hawaii:*	"This chapter applies to disease proximately caused by employment or resulting from the nature of the employment."
10. *Commonwealth of Philippines:*	"Grounds for compensation . . . any illness directly caused by such employment or the result of the nature of the employment."
11. *U. S. Longshoremen's and Harbor Workers' Act:*	(This applies also to employees of private employers in the District of Columbia.) "Injury means accidental injury . . . and such occupational disease or infection as arises naturally out of such employment."

In *Massachusetts*, the law has no list of occupational diseases nor is there any "blanket coverage" clause. The legislature amended the law in July, 1941 so that contracting a contagious disease is a compensable injury if the hazard of contracting such disease is inherent in the employment. The effect of this amendment is to make Massachusetts the only state without statutory "blanket coverage" in which occupational tuberculosis in hospital personnel is a compensable disease.

In *Minnesota*, there is a clause which applies to state hospital employees only. It requires preëmployment examinations for tuberculosis. If tuberculosis of occupational origin subsequently develops, compensation must be paid.

Connecticut is usually classed among states that have blanket coverage, but there is a limitation in the Connecticut Law which is rarely of consequence, except in tuberculosis. The Connecticut Law defines an occupational disease which is to be included in the law, as one "peculiar to the occupation in which the employee was engaged and due to causes in excess of the ordinary hazards of employment as such." The Connecticut Industrial Commission considers that tuberculosis in a hospital employee does not come within this definition.

An acceptable medical definition of occupational disease should not vary according to locality. The law does vary; it prescribes which occupational disease shall be compensable. Theoretically, in states with complete occupational disease coverage there would be compensation for all occupational diseases and for no others, if the administrators of the compensation laws were medically well advised. I say "theoretically" because these laws include diseases to which people are commonly exposed both in and outside of employment. Practically, in an individual case, it may be impossible for the medical adviser to distinguish between what is of occupational origin and what is the result of the normal

hazards of living. As uncertainties are generally resolved in favor of an occupational claim, some nonoccupational condition may at times be called occupational. On the other hand, with the limitation applied in Connecticut, some occupational diseases will be excluded. These will be the few occupational diseases which may originate either in the occupation or outside of employment. Tuberculosis is one of them.

SILICOSIS

Silicosis is a compensable disease in Idaho, Maryland, Michigan, North Carolina, Pennsylvania, Utah and Washington. In West Virginia and Kentucky an employer may elect to have his employees covered for silicosis. In these states, in the jurisdictions with "blanket coverage," and in Massachusetts compensation must be paid for tuberculosis if it is secondary to and caused by silicosis.

PRECEDENT AND EXPERT OPINION

If a higher court has made a decision on a question of law (for example, whether charitable institutions come under the compensation law), the lower courts usually accept this as a binding precedent and make similar decisions in all similar cases. The first decision acquires some of the characteristics of law. There is no such thing as precedent in medical testimony (or in any question of fact). Let us assume that physicians considered a dermatitis arising under certain conditions of work as nonoccupational and that a decision was rendered accordingly. Any time another claim arises and a physician has new or additional evidence or is of the opinion that the conclusions drawn in the preceding case are not warranted, hearings are held with reconsideration of all medical questions. Physicians can change the status of any disease from nonoccupational to occupational (or *vice versa*), provided they have sound evidence and are willing to present it in specific cases before the proper authorities. For a physician to report a disease as occupational or nonoccupational "because the compensation authorities have previously made such a decision" is, in effect, an evasion of his own responsibilities. If the physician has no opinion on the aetiology or is uncertain, he should so state, and defer to other physicians whom he accepts as authorities. A physician must never defer to legal decisions based on testimony with which he is not directly familiar or with which he is not in complete accord.

WHEN IS TUBERCULOSIS A COMPENSABLE DISEASE?

Compensation is payable for tuberculosis whenever it is:

1. Caused by an injury which in itself is compensable. This applies wherever there is a compensation law.
2. Caused by an occupational disease which in itself is compensable. This applies in states which have either "blanket coverage" or an occupational disease schedule, and also in Massachusetts.
3. Caused by occupational contact with tuberculosis patients or bacilli. This

applies in federal jurisdiction, in states and territories which have "blanket coverage," and also in Massachusetts where "personal injury" includes the contraction of communicable disease by occupational contact.

WAYS BY WHICH COMPENSATION LAWS CHANGE

By extension of the law more occupational diseases may be included among compensable diseases. The law may be extended by judicial interpretation of the term "accidental injury" to include the infection of a communicable disease. Such interpretation is not possible in the twenty-two states, and Alaska, which specifically exclude occupational disease. In any state the law may be extended by legislative action. Such legislative extensions have been made in various states and will probably continue to be made. If, in any state, a disease known and stated by physicians to be occupational is not compensable that is so because of the state's legislation. If a disease is legally adjudicated as compensable, when under the circumstances it is in fact not occupational, the fault lies with the medical testimony.

Legislative action to extend the compensation laws may take the form of (*1*) adding a schedule of occupational diseases where only injuries are now compensable; (*2*) amplifying and adding to an existing schedule; (*3*) adopting a general or "blanket coverage" clause for occupational diseases; (*4*) making the compensation law compulsory if now elective; (*5*) including employments now excluded.

Compensation laws have been a major factor in progress in discovery, treatment and prevention of occupational disease. When physicians fail to recognize the occupational origin of a disease, its prevention is obviously impossible. What happens when a nonoccupational disease is incorrectly classified as due to occupation on the basis of a physician's erroneous testimony? Though the effect may be less obvious, disease prevention is similarly made impossible. The erroneous classification establishes a fictitious origin and the industrial physician combats that chimera of occupational hazard while the ignored real cause continues to produce disease.

The whole structure of compensation law and occupational health rests on the medical data. Physicians should taken an interest in these laws and their administration just as they do in other public health activities. Physicians particularly are charged with the duty of discovering and formulating medical data and deciding on the relationship of disease and occupation. All compensation laws acknowledge that physicians are the sole authorities in this field. That supreme position will be maintained as long as physicians accept the responsibility which goes with it.

BIBLIOGRAPHY

(1) U. S. Federal Employees Compensation Act.
(2) U. S. Longshoremen's and Harbor Workers' Compensation Act.
(3) Compensation Laws of the various states and of Hawaii, Puerto Rico, Philippines and Alaska.

(4) Brahdy, L.: Occupational and Compensable Disease, Indust. Med., April, 1942, *11*, 147.

(5) Brahdy, L., and Kahn, S.: Trauma and Disease, 2nd ed., Lea & Febiger, Philadelphia, 1941.

(6) Dawson, M.: Problems of Workmen's Compensation Administration, Bull. No. 672, Bureau of Labor Statistics, U. S. Department of Labor, 1940.

(7) Dodd, W. F.: Administration of Workmen's Compensation, The Commonwealth Fund, New York, 1936.

(8) Koontz, E. R.: Compensation for industrial injuries and occupational diseases, J. A. M. A., February 17, 1940, *114*, 563.

(9) Mack, M. G.: Medical and Legal Phases of Tuberculosis as an Occupational Disease and as an Accidental Injury, Monograph, Social Research Series No. 6, Nat. Tuberc., New York, 1938.

(10) Sappington, G. O.: Medico-Legal Phases of Occupational Diseases, Industrial Health Book Company, Chicago, 1939.

(11) Teleky, L.: The compensation of occupational diseases, J. Indust. Hyg. & Toxicol., 1941, *23*, 353.

TUBERCULOSIS IN COLLEGE STUDENTS[1]

A Second Five-Year Review

CHARLES EVERARD LYGHT[2]

The passage of five years, or ten, has not removed the threat of tuberculosis from American college campuses. Tuberculosis clings tenaciously to first place among causes of death in those of college age. Nevertheless, the last five years have witnessed the appreciation of this fundamental fact by hundreds of colleges previously not impressed by the menace. As a result, it is fair to assert that, on many of the nation's campuses, tuberculosis is being dislodged from its position of vantage. If appropriate action can be stimulated in the remainder of our halls of higher education, investigators who conduct future five-year surveys should be able to report the gradual, eventual eradication of the disease from the academic scene.

Five years ago, in Milwaukee, a college hygiene session similar to this Philadelphia gathering heard with enthusiasm the encouraging summary presented by Dr. Lee H. Ferguson, of Western Reserve University. During his tenure as chairman of the Tuberculosis Committee, between 1931 and 1936, Doctor Ferguson and his colleagues had so popularized the idea of case-finding that the rapid enrollment of new institutional programs annually was already well under way. The sound principles selected by the original Committee and the strong organization they established have allowed us who came later to add to the structure with full assurance that the foundation would support an unlimited load. It is the realization that the edifice is far from complete that renders me anxious to hand on to the continuing builders not merely a blue-print, not merely materials and willing hads, but a share of the early vision. In a wartime period when many a building project must await happier days, nothing must be allowed to interfere with the erection of a veritable Temple of Health in which to house American education.

It has been stated that when the Tuberculosis Committee was formed in 1931 only a scant handful of American colleges and universities had taken cognizance of the menace to student health represented by tuberculosis. Six institutions were known to have begun programs—programs that were admittedly far from elaborate, but which acted as the leaven in the lump, and to which we can point proudly as marking the pioneering phase of case-finding in colleges. When the scroll of honor finally is written, Minnesota, Western Reserve, Yale, Michigan, Vassar and Pennsylvania will lead the list, but this roster would be meaningless if it did not at once conjure up such other names as Myers, Emerson, Forsythe, Ferguson, Lees, Kleinschmidt, Soper, Chadwick, McPhedran and Long, only to mention a few to whom we owe so much.

[1] Presented before the ninth annual College Hygiene Luncheon at the 38th annual meeting of the National Tuberculosis Association, Philadelphia, Pennsylvania, May 8, 1942.

[2] Director, College Health Service, Carleton College, Northfield, Minnesota.

Considering, then, that the history of case-finding in colleges goes no further into the mists of antiquity than the founding of Minnesota's first chest clinic for students twenty-two years ago, that the first formal search for tuberculosis among apparently healthy students began under Myers only fourteen years ago and that the Tuberculosis Committee has presented but ten annual Reports (exclusive of its preliminary statement of aims), it is both heartening and amazing that we now can point, not to 6, as when the First Five Years began, not to 50, as when that epoch ended, but to 304 colleges with programs operating during the academic year of 1940–1941.

Political experts tell us an organized minority may succeed in initiating and carrying to completion movements of national scope and import, even while the unorganized, though directly affected, majority remains unaware of what is afoot. I like to think of the Tuberculosis Committee and its friends as a "pressure group" of the right variety, lobbying tirelessly for health, pulling every legitimate wire to accomplish the elimination of a preventable, wasteful, often fatal disease. Instead of writing to senators and congressmen, we prevail upon college presidents and physicians, we solicit the support of coworkers in public health and tuberculosis control. That the campaign is succeeding is revealed by the further advances reported in this Second Five-Year Review that resumes the accounting where Ferguson's recapitulation of the First Five Years left off.

Whereas chart 1 demonstrates graphically the steady growth in the number of colleges sponsoring tuberculosis programs since the start that dated from the Syracuse Conference in 1931, table 1 brings out the details of how the movement is progressing sectionally. Comparing the first year and the fifth year of this second series of five, we find the number has almost tripled, so that last year we claimed enlistment of nearly 36 per cent of the country's colleges, as against 12.6 per cent in 1936–1937. New England, the section leading the list at the beginning, is still out in front, while the Southern section, now as then, trails the others. It is noteworthy, however, that the work in the 7 Southern states, though still very incomplete, has quadrupled during the five-year span. The greatest numerical increase has occurred among the numerous colleges in the 14 states of the Northern portion of the Mississippi basin.

Another interesting analysis is presented in table 2 where the rise in programs is broken down into the several types of institutions reporting. It will be observed that an almost unfaltering improvement has been evident annually in each category. However, some of the groups, such as that containing the State universities, have now neared their saturation point, while others, notably that including the endowed colleges, have a long distance to cover before all the potential members become actual volunteers. There is little doubt that financial considerations enter the picture at this point, along with sectarian, geographical and other less tangible factors. Attention should be directed to the challenging possibilities in the group of teachers' colleges and normal schools, thronged with those who will educate young America and shape the public opinion of the future. If they know the facts about health, they will not stand idly by and see it neglected.

There are certain portions of table 3 that call for comment. Of the 91 colleges employing the tuberculin test in 1936–1937, 88 per cent used the Mantoux intracutaneous technique. In the fifth year we note that the Mantoux method is being used in only 82 per cent of the tuberculin testing group. This drop must be charged against the recent experiments in some localities with patch testing, along with some schools using the Pirquet method because the State supplies only that type of testing material. I have felt that the patch test,

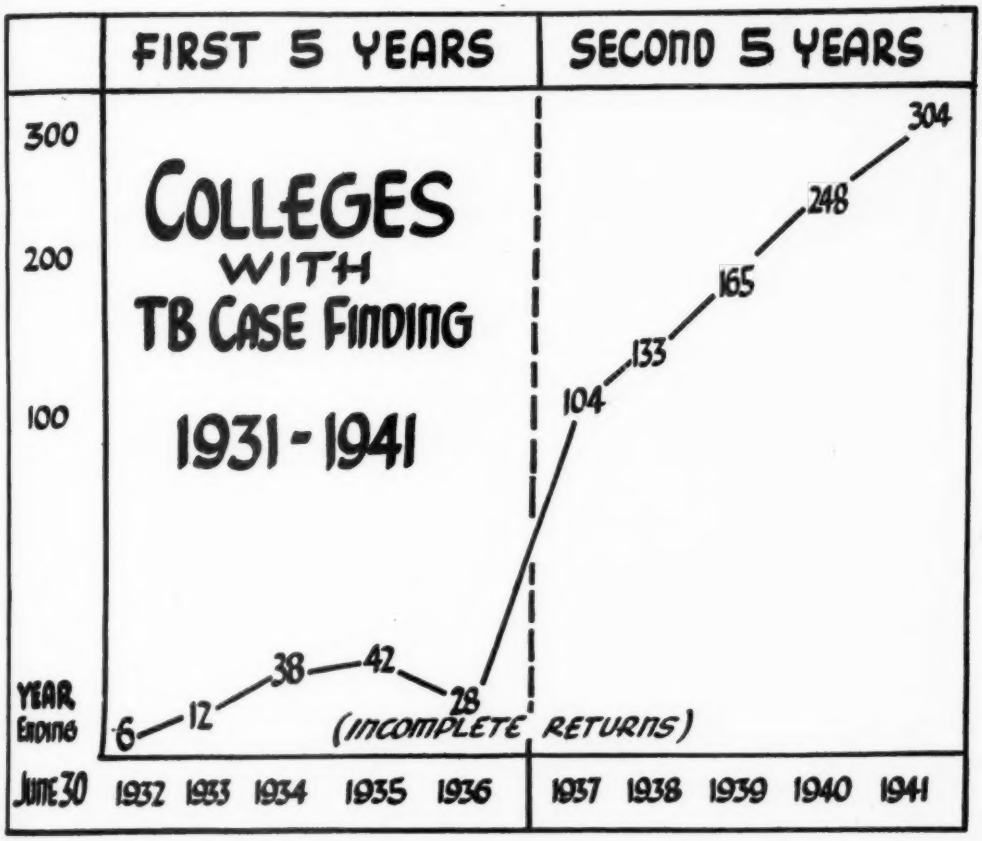


CHART 1

as revealed by personal experience, by many published reports and by the results forwarded to the Committee from scattered sources, cannot be recommended as a method as reliable for testing adults as is the accurately measured, safely administered, intracutaneous Mantoux test. I know, further, that the Committee, when polled last year, remained unanimously in favor of the Mantoux technique.

The Purified Protein Derivative of tuberculin, as in every year since its advent, remains by a small margin the testing material of choice, 55 per cent of the col-

leges using it in 1940–1941 at the close of the five-year period, 54 per cent employing it at the period's inception. The Committee has recommended PPD ever since it became available in 1934, but has also indicated that a good, reliable brand of Old Tuberculin, carefully standardized, will offer a satisfactory alternative for those schools whose budgets cannot provide the much preferable but more expensive PPD.

TABLE 1

Prevalence of tuberculosis programs in American colleges

REGION	NUMBER OF STATES	TUBERCULOSIS PROGRAMS IN		RATIO OF INCREASE
		1936–37	1940–41	
		per cent	*per cent*	
New England	6	18.4	50.0	2.7
Mountain and plateau	8	17.8	45.1	2.5
Mississippi Basin	14	14.4	41.3	2.9
Pacific Coast	3	16.6	39.3	2.4
U.S.A.	48	12.6	35.8	2.8
Central Atlantic	5	12.8	33.9	2.6
Southern Atlantic	5	8.8	31.1	3.5
Southern	7	3.4	13.3	3.9

TABLE 2

Number of colleges with tuberculosis programs

TYPE OF INSTITUTION	1936–37	1937–38	1938–39	1939–40	1940–41	RATIO OF INCREASE
Endowed colleges	36	41	58	105	118	3.3
Endowed universities	8	14	20	20	35	4.4
State universities	15	19	24	30	36	2.4
State colleges and institutes	12	18	19	22	35	2.9
State teachers' colleges	31	38	37	65	70	2.3
Civic colleges and universities	2	3	7	6	10	5.0

TABLE 3

Data on tuberculin testing

	1936–37	1940–41
Colleges with tuberculosis programs	104	304
Number employing tuberculin test	91	255
Per cent using Mantoux method	88	82
Per cent using PPD	54	55
Per cent reporting adequate dosage	48	60
Total students tuberculin tested	56,224	149,744
Per cent reactors found	27.3	20.7

The Committee's insistent recommendation of an adequate dosage of PPD or OT has not fallen entirely on deaf ears. In place of the 48 per cent of tuberculin testing colleges five years ago, using what we have held to be a sufficient dosage to find practically all reactors, last year found 60 per cent following this approved procedure. Despite the bother of a two-dose method, I feel persuaded that the most scientific and clinically accurate testing is being done in places where a minute preliminary dose is administered to weed out the highly allergic few, followed by retesting of the many nonreactors with a second strength dose that reaches 1 mg. of OT or 0.005 mg. of PPD. If a compromise intermediate dosage is to be tried, experience suggests that it should be not less than 0.002 mg. of PPD.

The number of students on whom tests were reported in 1936–1937 was 56,224. In 1940–1941 the total had swelled to 149,744. At the same time the percentage of reactors had decreased from 27.3 per cent to 20.7 per cent, although it is conceded that this latter figure may suffer from a mild diluting effect from inclusion of some patch tests and tests with incomplete dosage. The steady decline in the incidence of infection as shown by the response to tuberculin is a

TABLE 4

Analysis of X-ray procedures

PROCEDURE EMPLOYED	1936–37	1940–41
	per cent	*per cent*
Annual chest film for all reactors	20	28
Fluoroscope used to supplement films	10	15
Routine chest films without prior tuberculin testing	12	16

real diminution, however, as it has appeared in every annual Report of the Committee since 1932. As stressed in previous communications, the trend is more important than the fact that percentages must remain, at best, approximate.

The salient points brought out by table 4 are that the optimum and repeatedly urged annual chest filming of all reactors has advanced from 20 per cent of the tuberculin testing schools five years ago to 28 per cent last year. The use of the fluoroscope to reinforce the information gained from chest films has become 15 per cent rather than 10 per cent of the colleges in this group. Coincidently, however, we see that there are rather more than less colleges now than five years earlier, in which students are directly X-rayed without recourse to a prior tuberculin screening. The exigencies of many local situations may have dictated such a policy, and I well know that a clinician or a public health administrator must face the delicate but practical decision of how to make his available funds protect the greatest possible number of people. Whenever there is no good reason for side-tracking tuberculin testing, however, I am of the opinion that fancied short-cuts actually traverse insecure ground. For only by the discovery of all reactors to tuberculin can we know whom to observe as the infected individuals in a community.

Tuberculin testing, therefore, is finely discriminatory. It is well attested that X-ray evidence of very early pulmonary tuberculosis is seldom gross enough to be recognizable by standard filming. By noting the change of a nonreactor to an allergic person, we can form an accurate estimate of the time, often of the source, of his infection. If, on the other hand, we wait for unsupported roentgenographic evidence to accumulate to the point where suspicious film shadows result, valuable time may be lost, repeated scrutiny may be neglected, epidemiological opportunities may be missed. The safest, soundest surveys will include tuberculin testing, while in areas where reactors are scarce, they are also the most economical.

Opposed to this sound but pure theory are the practical results being achieved currently in such mass surveys as those conducted by the armed forces, in industry and by various public health agencies, using miniature films. Any method that leads to more persons being examined than ever before and examined reasonably effectively, is in the interests of prevention and opposed to the security of tuberculosis among the population. Accordingly, such a method is one to use, one to improve upon and not one to dismiss because it carries specific limitations. In the past five years a few colleges and universities have

TABLE 5

Tuberculosis case-finding among nonstudent personnel

	1936-37	1940-41
Number of colleges examining food handlers	30	108
Number of colleges examining faculty and administrative employees	29	92

adopted miniature film mass surveys. Scarcity of machines is likely to prevent more from experimenting with the innovation for some time to come.

In table 5 will be seen the encouraging results of five years of ceaselessly harping on the idea that those who wait upon students, work among them, feed them or teach them should be exhaustively scrutinized for evidences of tuberculosis in a transmissible stage. The number of colleges requiring their food handlers to submit to an examination has rocketed from 30 to 108, while those offering similar privileges to their faculties—always a vastly more ticklish proposition!—has reached 92, compared with 29 five years ago. The growth is laudable, the total number of colleges far from satisfactory. One infectious case of tuberculosis in a faculty member is infinitely more dangerous to a mass of students than would be one open case in a student to his occasional faculty contacts. To protect all, we must discover both.

The annual Reports of the Tuberculosis Committee have disclosed a startling difference in the amount of tuberculosis in students being discovered in colleges with case-finding facilities and in schools that answered our questionnaires but still lack a program. The cases reported in institutions where the disease is sought by modern methods are almost exclusively of the minimal variety,

whereas much of the tuberculosis coming to light in the second group of colleges is found only after symptoms drive the patient to apply for medical care or when demonstrable physical findings have developed due to advanced pathological processes. It need not be reëmphasized, surely, that cases in this latter category are no longer preclinical, but are moderately or far advanced in nature. The prognosis of such cases is obviously much reduced, the chances of their infecting others greatly multiplied. An equally deplorable condition undoubtedly exists in colleges from which we have not yet succeeded in eliciting a reply. It is ridiculous to presume that any college can be free of tuberculosis simply by deciding to ignore it completely.

The new cases of tuberculosis found during the last five years in the two contrasting groups of colleges are summarized in table 6. Colleges in group I, sending in returns, but claiming no measures in operation to find presymptomatic tuberculosis, have reported finding 184 new cases in a five-year enrollment that aggregated 668,895 students, or 27.5 previously unsuspected cases per 100,000. It must be borne in mind that this relates to "enrolled," not to "examined" students. Colleges in group II, participating in our survey for the past five

TABLE 6

Tuberculosis diagnosed (both active and arrested) among students, 1936–1941*

	ENROLLMENT (5 YEARS)	NEW CASES DISCOVERED	RATE PER 100,000 STUDENTS ENROLLED
Colleges with *no* formal program of case-finding.....	668,895	184	27.5
Colleges with *some* organized tuberculosis program.....	1,850,755	3,523	190.5†

* Excluding healed primary lesions.

† Of these, 39 per cent were clinically active.

years, and claiming case-finding embracing part or all of their total 1,850,755 students enrolled during the period, discovered no less than 3,523 new cases, thus establishing a rate of 190.5 previously undiagnosed cases per 100,000 enrolled. Roughly, this confers a ratio of seven-to-one in favor of the progressive colleges dedicated to the proposition that tuberculosis must be tracked down to its lair, found early, treated promptly, if it is to be defeated ultimately in the individual and in the nation. When we recall that all standard criteria were insisted upon, and that 2 out of every 5 of the new cases found in group II were diagnosed as clinically active, most leaving college to seek immediate treatment, it will be realized that these figures indicate the need for thoughtful consideration. They imply that thousands of cases of tuberculosis, many of them infectious, are being harbored and ignored among American college students through utter failure of most colleges to comprehend that a threat to health truly exists and that a major social and economic problem clamors for action.

A paragraph at this juncture containing the high-lights of statements received from dozens of ranking college administrators, as they have attempted to justify the nonexistence of a case-finding program on their respective campuses,

would not seem inappropriate, even though it might bear some resemblance to one lifted from a Book of Boners. I hesitate to include such a documented cross-section of misinformation, however, since the ignorance demonstrated might influence some to suspect I had lapsed into sarcasm or that I had attempted to call down ridicule on the heads of men and women whose problems, even apart from those based in student health, are legion, and whose intentions are of the best. Never in the five years I have been in a position to ponder such literarily perfect, medically pathetic letters have I sensed discourtesy, brusqueness or disinterest. All that is evident is an archaic conception of what tuberculosis is, how it acts and what can be done cheaply and easily to nullify its attacks on youth. The ancient idea that only when "consumption" arrives is tuberculosis present, the equally erroneous notion that early tuberculosis can be ruled out by a doctor's cursory certification or by stethescopic search or by stratified social selection, are still too rampant. These fallacies distress us as experienced health workers. But their survival among educated people represents only our failure to carry the truth ceaselessly and convincingly to every person whose information, no matter how complete in most directions, remains barren with respect to tuberculosis.

Kendall Emerson recently issued a ringing appeal that we unite to defeat the treacherous enemy, tuberculosis, within our own boundaries. The five-year period under discussion ended almost six months before our entry into the war, but no presentation would be complete without a reference to the future, the acknowledged opportunity for tuberculosis to show a sharp up-swing in the midst of war conditions that allow overcrowding and overwork, that disrupt private and public medical service, that curtail budgets and restrict facilities. Along with other agencies, it is inevitable that college health services will be deprived of much essential personnel, will feel the pinch of retrenchment. But it must never be said that we were not alert to the increasing menace of tuberculosis among our students, or that we failed to do everything humanly possible to maintain, yes, to go on advancing the quality as well as the amount of case-finding we had succeeded in building up before other enemies treacherously attacked us, diverted our attention and our energies, made us more vulnerable.

Just as counties were once accredited for eliminating tuberculosis from their dairy herds, even as they are today being accredited in Minnesota for driving death rates and infection rates to low levels, so, I believe, colleges and universities might be accredited by the American Student Health and the National Tuberculosis Associations, once they have inaugurated and maintained acceptably a modern program against student tuberculosis. I believe that this innovation would, with proper publicity, tempt laggard colleges to make the necessary adjustments so as to gain a place for their names on the proud Roll of Honor of progressive, public-spirited institutions.

The war must go on. The war must be won and we must win it, both from our external foes and from such borers-from-within as tuberculosis. It would be disastrous if the next Five-Year Survey that emerges at a college hygiene session in 1947 had to tell of lost ground, poorer standards, less interest, more tuberculosis.

Army, Navy, industry, public health—all must fight together and against tuberculosis. But it is of the very essence and function of education that colleges and universities lead the battle.

As we embark on our Third Five-Year Plan, let us be warned that tuberculosis still shows no sign of adopting the forty-hour week!

SUMMARY

Although tuberculosis has declined to seventh place in the list of death causes in the U.S.A., it remains the leading cause among those of college age. More and more colleges and universities have accepted responsibility for instituting and maintaining on their campuses modern methods of early diagnosis of tuberculosis.

At the conclusion of ten years' existence, the Tuberculosis Committee of the American Student Health Association presents a record of steady progress in its campaign to eradicate the disease from college students, food handlers and faculty and administrative personnel. This Second Five-Year Review reëmphasizes the Committee's insistence on a program that includes a tuberculin test for all, annual retesting of negative reactors, chest roentgenograms for positive reactors, painstaking clinical and laboratory follow-up of suspicious cases, and a back-tracking search for the sources of individual infections.

In 1931–1932 only 6 American colleges or universities sponsored case-finding. Five years later the number had grown to 50, while at the end of a decade of the Committee's effort, 304 institutions belonged in that category. Every region in the United States demonstrates improvement in its programs, both qualitative and numerical, so that in 1940–1941 approximately 36 per cent of the nation's colleges had up-to-date facilities. All types of colleges have participated in the advance, with greatest residual need in the small, financially poorer, private colleges.

The Mantoux intracutaneous technique with an adequate dosage leads in popularity, as does PPD as a testing material. X-ray methods vary from routine filming of every student to selective examination of the reactors, and employ standard-sized films generally, with microfilms in use in some places. Annual filming is the ideal procedure and is in vogue at 28 per cent of the colleges concerned.

A five-year growth in the number of tuberculin tested students from 56,224 to 149,744 has been accompanied by a gratifying fall in reactors from 27.3 to 20.7 per cent. Since 1936 the number of colleges providing for examination of their food handlers has climbed from 30 to 108, of faculty members from 29 to 92, indicating the gradual plugging up of unwarranted loopholes in student health protection.

The results of the unceasing battle are revealed by figures that show a seven-to-one ratio of student tuberculosis diagnosed favoring the colleges wherein it is being ferretted out by modern means, as compared with institutions in which it is found only when patients seek medical advice belatedly because symptoms have brought them to the college doctor. Encouragingly, cases turned up in the first group of schools are almost uniformly presymptomatic, promising most

in prognosis, demanding less prolonged treatment, financial loss or disturbance of educational and vocational plans, and minimizing the opportunity for spread of the disease to healthy students.

SUMARIO

Aunque la tuberculosis ha descendido al séptimo lugar en la lista de causas de muerte en Estados Unidos, continúa siendo la causa principal entre las personas de edad universitaria. Un número cada vez mayor de facultades y universidades se ha comprometido a iniciar y mantener en su recinto medios modernos para el diagnóstico temprano de la tuberculosis.

Al cumplir sus diez años de existencia, la Comisión Antituberculosa de la Asociación Americana de Higiene Estudiantil presenta una historia de constante adelanto en su campaña para erradicar la dolencia de los estudiantes, los manipuladores de alimentos, y el personal didáctico y administrativo en las distintas instituciones. Este Segundo Repaso Quinquenal hace de nuevo hincapié en el plan de la Comisión, que comprende la ejecución de una reacción a la tuberculina en todos los estudiantes, recomprobación anual de los negativos, roentgenogramas torácicos para los positivos sospechosos, y pesquisa de los focos causantes de los casos dados.

En 1931–1932 sólo 6 facultades o universidades de Estados Unidos auspiciaban la pesquisa de casos. Cinco años después el número ya había subido a 50, mientras que al terminar el decenio figuraban en esa categoría 304 instituciones. Todas las regiones de Estados Unidos han mostrado mejoramiento tanto cualitativo como numérico en sus obras, de modo que en 1940–1941 aproximadamente 36 por ciento de las universidades del país contaban con medios modernos. Los colegios de todo género han participado en el avance, pero todavía los que tienen más lagunas que colmar son los pequeños particulares y peor dotados económicamente.

La intracutirreacción de Mantoux a dosis adecuadas es la que disfruta de mayor popularidad, y lo mismo sucede con PPD como sustancia de ensayo. La técnica roentgenológica varía de la radiografía sistemática de todos los estudiantes, a un examen selectivo de los reactores y empleo general de las películas de tamaño corriente, aunque en algunos sitios utilizan los microfilms. La radiografía anual constituye el procedimiento ideal, y es utilizada en 28 por ciento de las instituciones interesadas.

Un aumento quinquenal de 56,224 a 149,744 en el número de estudiantes comprobados ha ido acompañado de una halagadora baja de 27.3 a 20.7 por ciento en los reactores. Desde 1936 el número de instituciones que examinan a sus manipuladores de alimentos ha subido de 30 a 108, y al el personal didáctico de 29 a 92, lo cual indica cómo se van llenando gradualmente las lagunas injustificadas en la protección de la salud de los estudiantes.

El resultado de la incesante batalla se refleja en las estadísticas que revelan una proporción de siete-a-uno de tuberculosis diagnosticada, en particular en las instituciones en que buscan el mal con medios modernos, comparado con

aquéllas en que no lo descubren más que cuando los enfermos solicitan tardíamente consejo médico porque los síntomas los hacen acudir al doctor. Es alentador observar que los casos descubiertos en el primer grupo de escuelas son casi siempre presintomáticos, y de los que prometen más en el pronóstico; imponen menos tratamiento prolongado, pérdida económica o trastornos de los planes educativos y vocacionales, y aminoran las probabilidades de propagar la enfermedad a los estudiantes sanos.

REFERENCES

(1) Annual Reports of the Tuberculosis Committee, Am. Student Health A., Seventh through Eleventh, Journal-Lancet, October, 1938, *58*, 451; April, 1939, *59*, 168; April, 1940, *60*, 178; April, 1941, *61*, 115; April, 1942, *62*, 125.

(2) Emerson, K.: The industrial front, Journal-Lancet, 1942, *62*, 111.

(3) Ferguson, L. H.: A five-year review of tuberculosis in college students, Am. Rev. Tuberc., 1937, *36*, 478.

(4) Shepherd, C. E.: A survey of American college student health services, Rep. Am. Youth Com'n, 1937.

TREATMENT OF TUBERCULOSIS WITH A LOW CARBOHYDRATE DIET[1]

BENJAMIN P. SANDLER AND RUDOLPH BERKE

INTRODUCTION

The purpose of this report is to describe the effect of a low carbohydrate, high protein diet on a group of patients with advanced pulmonary tuberculosis. From available experimental and clinical data, factual and theoretical, it was thought that such a diet could be beneficial in the treatment of tuberculosis because it would increase oxidations in the entire organism by removing the depressant effect of carbohydrate-rich foods on bodily oxygen consumption. An attempt will be made to show that the continued ingestion of a diet containing carbohydrate-rich foods, like any general hospital diet, may depress glucose-oxygen consumption by producing hypoglycaemia in non-diabetics, and by aggravating an already existing disturbance in carbohydrate metabolism in patients with tendency to hyperglycaemia. In tuberculous patients who showed neither hypoglycaemia nor hyperglycaemia according to the glucose tolerance test but who improved on a low carbohydrate diet just the same, an attempt will be made to show that the organism consumes more glucose and oxygen because such a diet probably makes available a more highly reactive form of glucose, labelled γ-glucose. It is also likely that a low carbohydrate diet brings about clinical improvement, maintains normal blood sugar levels, and increases glucose-oxygen consumption by bringing about and maintaining normal liver glycogen stores. Susceptibility to, and persistence of tuberculous infection, are very likely fundamentally related to the amount of gylcogen stored in the liver. For this reason good nutrition, physical and mental rest have been effective therapeutic measures in the treatment of tuberculosis. Rest is effective because it makes available for healing processes glucose and oxygen which might have been used for muscular energy.

Evidence that a high carbohydrate intake may favor the development of tuberculosis, and that a low carbohydrate diet may protect against tuberculosis, has accumulated from various sources. Faber (1), in an analysis of factors responsible for the increase in tuberculosis mortality in Denmark, Sweden and England during World War I, concluded that the reduced consumption of meat and fish was the most important nutritional factor. He writes:

"In Denmark the increase in tuberculosis mortality took place in 1916–1917 simultaneously with a greatly reduced consumption of meat and fish, and the decrease of the mortality coincided with a greatly increased consumption of these foods. If we take beef, veal, and fish alone, the fall in consumption was extraordinary in 1915–1916. The total calories consumed was not diminished because there was sufficient bread and flour." He continues, "We see the same thing in Sweden, though to a less marked degree. The rise

[1] From the Division of Pulmonary Diseases, Dr. Max Pinner, Chief of Division, Montefiore Hospital for Chronic Diseases, New York, New York.

in tuberculosis mortality was recorded in 1914–1916, and in those years the consumption of bread and flour rose, whereas that of meat decreased. After 1916 we see a steady and continuous fall in tuberculosis mortality, and at the same time flour foods fell off while the consumption of meat and particularly fish rose rapidly. It may be added that in England, too, a rise in tuberculosis mortality coincided with a lower consumption of meat and butter and an increased consumption of flour foods."

Weigert (2) found that guinea pigs fed a carbohydrate-rich diet and then inoculated with tubercle bacilli developed a much severer from of tuberculosis than did guinea pigs fed a carbohydrate-poor diet. Adlersberg and Porges (3) employed a low carbohydrate diet in the treatment of lung abcess, bronchiectasis and other inflammatory states. They attribute clinical improvement to the dehydrating and "antiphlogistic" effects of such a diet.

The continued consumption of carbohydrate-rich foods may cause susceptibility to infection because it may depress blood sugar levels, thereby reducing the delivery of glucose to tissues for utilization. This is analagous to the uncontrolled diabetic's susceptibility to infection; in both the end-result is a subnormal oxidation of glucose. McCullagh and Johnston (4) have shown how a continued high carbohydrate intake may depress blood sugar levels.

The rationale for a low carbohydrate diet in the treatment of tuberculosis was based on clinical observations and blood sugar studies made on a large group of patients with chronic hypoglycaemia and chronic hyperglycaemia successfully treated with a similar low carbohydrate diet. It had been found that a low carbohydrate diet elevated the blood sugar to normal levels in patients with hypoglycaemia (graph 1), lowered the blood sugar to normal or near normal levels in patients with hyperglycaemia, and stabilized the blood sugar in patients who showed wide fluctuations on a high carbohydrate intake (graph 2).

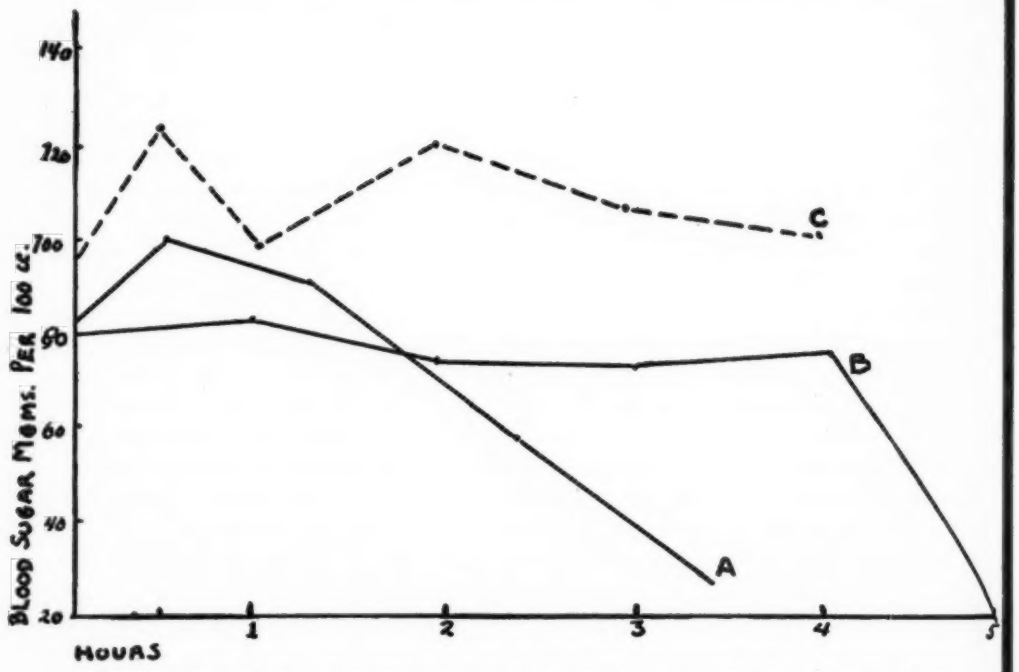
During these studies it was noted that patients on a low carbohydrate diet reported a reduction in the number of respiratory infections. Patients who were having frequent head colds reported fewer colds which were milder and shorter in duration. Patients subject to frequent attacks of grippe and bronchitis with persistent cough and sputum did remarkably well on such a diet. It seemed likely that the disturbance in carbohydrate metabolism could be a factor of susceptibility to respiratory infections, acute and chronic. In addition to relief from, and protection against respiratory disorders, these patients improved notably in regard to general health. They appeared more vigorous and buoyant.

Paton (5) reported a reduction in incidence of cases of catarrhal illness in a large boarding school for girls in England during World War I. He states that the factor responsible was the reduction in carbohydrate intake, especially sugar, during those years. Several houses in a boarding school for girls had different rates of sugar consumption, 1.2 to 2.2 pounds a week per head. The house with the lowest sugar consumption had a catarrhal rate of 5.5 per cent, while the house with the highest sugar consumption had a rate of 24.6 per cent.

Spiesman and Arnold (6) found in following a group of chronic head-cold sufferers that a low carbohydrate diet was the most effective means of reducing

the incidence of, and susceptibility to, the common cold. Investigations from the Rowett Research Institute (7) have recorded that a study of the diet and health of two East African tribes revealed that the mortality from bronchitis and pneumonia was ten times as great in one tribe which was cereal eating, as it was in the other which was carnivorous in habit.

Physiological considerations: Patients with these disturbances in carbohydrate metabolism suffer because of a reduced glucose utilization. In hypoglycaemia there is insufficient glucose delivered to tissues for utilization. In hyper-

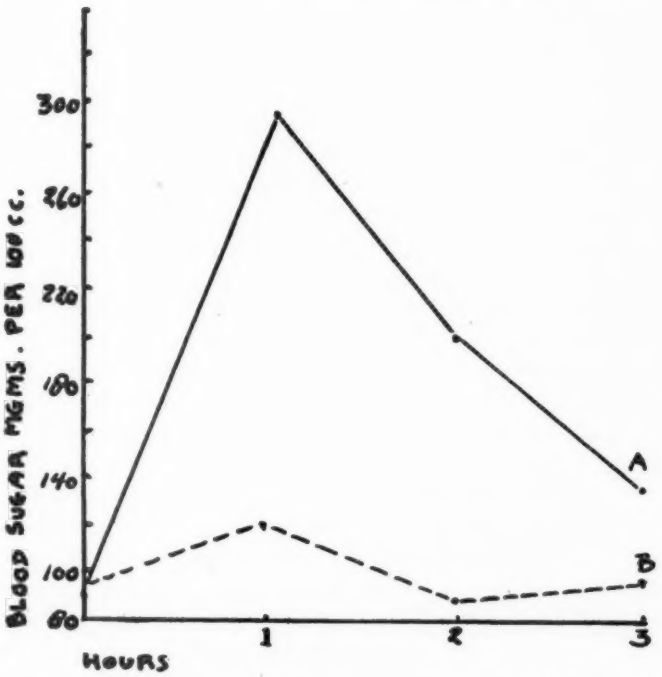


GRAPH 1. The effect of various meals on the blood sugar in a patient with chronic hypoglycaemia. Curve A shows course of the blood sugar after 100 g. glucose; curve B shows the course after a high carbohydrate meal consisting of one orange, a bowl of oatmeal, two rolls, and a cup of sweetened coffee; curve C shows the course after a low carbohydrate meal consisting of one orange, two eggs, one thin slice of bread and butter, a glass of milk to which was added 1 oz. of cream. About two hours after this meal the patient took a glass of milk.

glycaemia (diabetes) the glucose is not being utilized in normal quantity. Since it has been established that tissues utilize oxygen in proportion as they utilize glucose, it is evident that in the presence of reduced glucose utilization there is an actual tissue asphyxia of varying degree depending on the severity of the metabolic disturbance. Dameshek, Myerson and Stephenson (8) found that during insulin hypoglycaemia in man there was a diminished oxygen consumption by the brain. Himwich and Fazekas (9) found that during insulin hypoglycaemia in dogs there was a diminished oxygen uptake by the brain. Holmes (10),

Dickens and Greville (11) and Wortis (12), using the Barcroft-Warburg technique, found that the oxygen uptake of excised pieces of brain, spinal cord, heart, testis, kidney and spleen fell as the amount of glucose in the nutrient medium was reduced.

In addition to the chronic reduction in glucose-oxygen consumption as a cause of symptoms, patients with these disorders may suffer because of wide fluctuations in blood sugar concentrations with periods of rapid fall to absolute or relative hypoglycaemic levels. During such periods of rapid fall, symptoms such as headache, dizziness, faintness, nervousness, tremors, sweating, pallor, flushing,



GRAPH 2. Curve A shows course of the blood sugar after 100 g. of glucose; note marked hyperglycaemia, with sharp rise and fall. Curve B shows the course after a low carbohydrate meal; note that all values are within normal range. Note that the fasting blood sugar values are normal.

palpitation, tachycardia, abdominal pain and psychoneurotic manifestations may occur. A rapid fall in blood sugar from 200 mg. to 150 mg. in a diabetic will cause symptoms exactly like those occurring in a non-diabetic who experiences a fall from 100 mg. to 50 mg. Headache, dizziness, faintness and psychoneurotic manifestations may be attributed to the effect of the fall in blood sugar on the brain itself. Since the central nervous tissues burn glucose exclusively for energy purposes they are extremely vulnerable to sudden changes in blood sugar levels. Symptoms such as nervousness, tremors, sweating, pallor, palpitation and tachycardia are due to adrenal-sympathetic stimulation occasioned by the fall

in blood sugar, a protective mechanism which comes into play at hypoglycaemic levels (13). These sympathetic symptoms may be regarded as unpleasant side-reactions accompanying the essential glycogenolytic action of adrenalin.

A low carbohydrate, high protein diet restores the blood sugar to more normal levels. Clinical improvement may be attributed to an increased glucose-oxygen consumption on such a diet. Further, it is very likely that such a diet, paradoxically, actually increases liver glycogen stores to more normal levels in patients where a subnormal storage exists. Since the breakdown of liver glycogen is the ultimate source of the blood sugar, a well stocked liver is essential to normal carbohydrate metabolism. This holds true for the non-diabetic just as it does for the diabetic. Since glucose is by far the most important source of energy, the need for adequate glycogen stores is obvious. Glucose is needed not only for heat production and muscular activity, but also for protection against infection. Richardson (14) concluded that "under-fed rabbits with depleted liver glycogen developed definitely lower agglutinative titre after typhoid vaccine than did well fed controls with higher liver glycogen." He also found a "significant correlation to exist in normal rabbits and depancreatized cats between the percentile amount of glycogen in the liver and the survival time after intravenous inoculation with bacteria" (15). Control of the diabetic with diet and insulin brings about an increase in liver glycogen stores and enables him to resist infection. By the same token susceptibility in the non-diabetic may result from inadequate liver glycogen stores with resultant subnormal glucose-oxygen consumption.

In the case of the patient with hypoglycaemia the reduced glucose delivery to tissues results in a reduced glucose-oxygen consumption. This resultant tissue asphyxia may lower the resistance of the organism to bacterial invasion. A chronic hypoglycaemia may thus favor the development of a disease such as tuberculosis. Variation in the degree of the metabolic disturbance will influence the severity and course of the infection. An acute disturbance in carbohydrate metabolism, such as would accompany a short period of hypoglycaemia, may be responsible for the onset of an acute infection such as poliomyelitis. Sandler (16) was able to produce necrotic lesions in the anterior horn cells of rabbits with the virus of poliomyelitis by inoculating rabbits during insulin hypoglycaemia. The rabbit is ordinarily resistant to the virus. This resistance has been attributed to the fact that its blood sugar never falls below 100 mg. per 100 cc.

During fasting the blood sugar is maintained at around 100 mg. per 100 cc. by the liberation of glucose from liver glycogen. Cori (17) states that the blood sugar of mammals is normally maintained at 100 mg. per 100 cc. Such glycogen stores arise from the ingestion of carbohydrates and proteins. It is estimated that about 58 per cent of protein and possibly 10 per cent of fat is available for conversion to glucose. Normal blood sugar levels may be maintained on exclusive protein and fat diets because of this conversion, and the blood sugar on such a diet is obviously wholly derived from liver glycogen. Such endogenous glucose is to be differentiated from exogenous or preformed glucose that is present in the blood stream after ingestion of glucose or carbohydrate-rich foods.

This distinction is important because there is evidence that the organism metabolizes endogenous glucose more efficiently than it does exogenous glucose. In 1912 Benedict and Joslin (18) wrote:

"The possibility of the combustion of sugar derived from protein should be carefully noted. The non-nitrogenous portion of the protein molecule seems to be tolerated in many instances by diabetics better than preformed sugar. It is conceivable, for example, that it may be of distinct benefit to have large amounts of protein ingested and thus have the carbohydrate moiety of the protein molecule broken down, perhaps in some different manner or different portion of the body than would be the case in ordinary absorption of carbohydrate from the intestine. . . .Without doubt the ingestion of meat does stimulate the metabolism. . . . If, in addition to the stimulated metabolism, we have the liberation of non-nitrogenous material in certain parts of the fluids of the body which may prove to be of special benefit, we have a double reason for the ingestion of large quantities of protein."

This preference of the organism for endogenous over exogenous (preformed) sources of energy is not confined to glucose, but is also true of amino-acids. Weiss and Rapport (19) discovered that there was no increased specific dynamic action when 10 g. of glycin or 10 g. of alanin were added to 40 g. of either gelatin or casein. Rubner (20), in an attempt to explain this behaviour of the artificially prepared amino-acids, suggested that "perhaps the cells prefer the natural product to the artificially prepared material." Lusk (21) further added that under these circumstances the ingestion of the artificially prepared glycin "would find a different path of destruction from the one usually followed."

It thus appears that the organism can utilize more readily glucose and amino-acids that are elaborated in the course of metabolic processes than glucose and amino-acids ingested in the preformed state.

Several biochemists and physiologists have long suspected the existence of a highly reactive form of glucose which they have labelled γ-glucose and which is not present in the ordinary solutions of glucose. The evidence for its existence, while indirect, is strong. It has been stated that the organism converts ordinary glucose to this reactive form as a preliminary to oxidation, a power lacking in the diabetic (22). Shaffer (23), in a review of the literature, has stated: "From the evidence cited the hypothesis appears attractive that α-β-glucose is converted under the joint influence of tissues and pancreatic hormone into γ-glucose, which may then be polymerized to glycogen or transformed into other derivatives capable of oxidation, both of which fates are closed to the molecular configurations of ordinary glucose." Levene (24) has also presented evidence for the existence of both "active glucose" and "active triose."

In the fasting state the blood glucose is obviously derived from the liver and may be said to exist entirely in the reactive endogenous form. Similarly, on a protein-fat diet, the blood glucose is derived solely from liver glycogen. Since the normal rate of discharge of glucose from the liver is such as to maintain the blood sugar of mammals at around 100 mg. per 100 cc., it is evident that tissue oxidations will be at normal levels if such a sugar level is maintained. The ingestion of carbohydrate-rich food or glucose is followed usually by a rise in

blood sugar, but not necessarily by an increase in oxygen consumption since the influx of exogenous glucose is apparently not easily oxidized and must be converted to the γ-form directly or be synthesized to glycogen in the liver and then liberated as glucose. That the exogenous sugar is not readily oxidized is evident from the observations made on normal human subjects by Benedict and Carpenter (25). These workers observed that after ingestion of carbohydrate there was a smaller consumption of oxygen than after protein. In some experiments there was an actual fall in oxygen consumption after carbohydrate, a phenomenon which they were unable to explain. For example, they fed one subject 400 g. of bananas (413 calories) and observed an increase in oxygen absorption of 5.5 g. during the first hour, and a fall in oxygen absorption during the second, third and fourth hours. In the same subject, after 217 g. of beefsteak (451 calories) there was an increase in oxygen absorption during each of four hours, with a total increase of 17.5 g. as against a net increase of 1.5 g. after the bananas. Numerous similar results were obtained by Benedict and Carpenter. With larger meals the results were even more striking. For example, after 1,382 calories of a maltose-dextrose mixture there was a fall in oxygen absorption of 11 g. over an eight-hour period, that is the subject would have absorbed 11 g. more oxygen if he had fasted for the eight hours. On the other hand, after 1,305 calories of beefsteak, there was an increase in oxygen absorption of 46 g. for an eight-hour period.

Before attempting to offer some explanation for this smaller oxygen consumption after carbohydrates, it is necessary to consider recent important discoveries made by Soskin and coworkers on the rôle the liver plays in blood sugar regulation (26, 27). Soskin and coworkers have shown that the liver output of glucose is suppressed when glucose is injected intravenously, that is when there is an influx of exogenous glucose. As the blood sugar returns to its previous level the output is resumed. Further, it was noted that the suppression was greater and lasted for a longer time when the amount of glucose was increased. The suppression may be so great as to bring about a lag in resumption of output and cause a hypoglycaemia. Soskin concluded that this phenomenon readily explained clinical hypogycaemia and demonstrated that this hypoglycaemia could occur in the absence of an extra discharge of insulin.

What is of great significance, then, is the fact that following the ingestion of carbohydrate, the liver output of (endogenous) glucose is suppressed to a greater or lesser extent depending on the amount of carbohydrate ingested. If the hypothesis that this liver glucose is the highly reactive γ-form is correct, then during such suppression the organism will consume less oxygen, even though there is a rise in blood sugar due to the influx of exogenous glucose. This may explain why Benedict and Carpenter observed little or no rise in oxygen consumption after ingestion of carbohydrate in some experiments and why there was an actual decrease in oxygen consumption in other experiments. When protein is ingested there is no such suppression of liver output of glucose. The greater oxygen consumption after protein may thus be attributed in part to a greater glucose utilization because the liver output of glucose will be undisturbed

and there will be oxidation of glucose resulting from the conversion of amino-acids.

Any such interruption in the discharge of glucose from the liver may be regarded as unphysiological in that it may bring about a reduced glucose and oxygen consumption. Except for the rare cases of hypoglycaemia due to islet cell tumors, it is likely that most cases of chronic hypoglycaemia are due to abnormalities in the rate of discharge of glucose from the liver as suggested by Soskin and his coworkers. The hypoglycaemia may be said, therefore, to depend on two factors: the amount of glycogen stored in the liver and the rate of discharge of glucose from the liver, which, in turn, will depend on the amount of exogenous glucose ingested.

When patients with hypoglycaemia go on a low carbohydate diet the general level of the blood sugar is maintained at around 100 mg. per 100 cc. This rise in blood sugar may be attributed to the fact that the inhibitory influence of a high carbohydrate intake upon the liver output is removed.

In the case of patients with hyperglycaemia (who are to be regarded as mild diabetics) there is reduced glucose utilization because of the inherent nature of the disorder. These patients also improve on a low carbohydrate diet. One is forced to conclude that there is greater glucose-oxygen consumption on such a diet with normal blood sugar levels than on a high carbohydrate diet with hyperglycaemic levels. On a low carbohydrate diet the blood sugar is obviously derived chiefly from the liver and may be said to exist in the reactive γ-form.

Patients with hyperglycaemia have a severer disturbance in carbohydrate metabolism than hypoglycaemic patients because, in addition to the fundamental impairment in the handling of carbohydrate-rich foods, there is the unfavorable depressant effect by carbohydrate-rich foods on the output of glucose from a liver which, in the untreated diabetic, is usually poor in glycogen. For this reason hyperglycaemic patients should not eat any carbohydrate-rich foods even if they are receiving insulin.

The incidence of abnormal tolerance curves in patients with pulmonary tuberculosis has been shown to be high. Kramer (28) did 100 tolerance tests on 100 patients with pulmonary tuberculosis. He found 41 to have abnormal curves; 17 showed the hyperglycaemic type and 24 showed the hypoglycaemic type of curve. The remainder apparently had normal curves.

The constant demand by the tissues of the body for glucose for energy purposes necessitates a constant source of supply. Failure of this supply mechanism results in death. If the supply of glucose fails, whether because of a hypoglycaemic state, or because of a severe diabetic state in which glucose utilization is greatly impaired presumably because the supply of γ-glucose is very low, the body will draw on its own tissues (muscle and fat) to get glucose. Under such circumstances these tissues break down yielding split-products which can be synthesized to glycogen in the liver and then paid out as glucose. Such endogenous glucose may be said to exist in the reactive γ-form. If this state is prolonged, emaciation supervenes. Emaciation in severe tuberculosis indicates severe impairment of the carbohydrate metabolism.

SELECTION OF PATIENTS

In selecting cases for the first clinical trial of the diet in pulmonary tuberculosis, only such patients were selected who were not fit for any form of collapse therapy and whose prognosis appeared to be quite poor. Seven representative case histories follow.

Case 1: H. P., white male, age fifty-seven, a jewelry salesman, was admitted to the Montefiore Hospital in July, 1940. He had been coughing for many years. A diagnosis of pulmonary tuberculosis was made in June, 1940, when he had an exacerbation of symptoms. On admission he was pale and dyspnoeic on slight exertion. He also had attacks of dyspnoea at rest. He had severe cough and expectoration, weakness and anorexia. The sputum was purulent, 80 to 200 g. daily, and was consistently positive for tubercle bacilli. He had much belching after meals. He weighed 98 pounds. He was irritable, nervous and easily provoked. Physical and roentgen examination indicated far advanced bilateral pulmonary tuberculosis, with a large cavity in each upper lobe (figure 1). He was considered suitable only for custodial care. After five months of bed-rest, aside from a gain of 5 pounds, there was no change in subjective symptoms and no change on X-ray examinations.

On December 16, 1940, a glucose tolerance test showed no abnormal blood sugar values. However, he was put on a low carbohydrate diet. Within two weeks a distinct improvement was manifest. He felt stronger and his appetite was better. He had less belching. His breathing was much lighter. He said he had more "pep and ambition." There was a decrease in cough and expectoration. His weight was stationary for two months and then began to rise. His face became fuller and had a better color. The sputum became frothy and less purulent.

Roentgenograms showed no change in the lungs until March 25, 1941, three months after going on the diet. The film on that day revealed increasing fibrosis of the upper lobes and the cavities were distinctly smaller. In July, 1941, for the first time, two sputum smears were negative for tubercle bacilli. Concentrated specimens of sputum in August and September were positive. In the ensuing months there was continued clinical and roentgenologic improvement. By December, after twelve months on the diet, he had gained 25 pounds. He had minimal cough and expectoration. After November 6, the sputum was negative on eight consecutive examinations, including concentrates. A chest film did not show the former cavities (figure 2). He was discharged December 16, 1941, virtually symptom free.

FIG. 1. Case 1. Upper left. Before diet. Large cavities in the upper lobes. Extensive bilateral infiltrations. Emphysema.

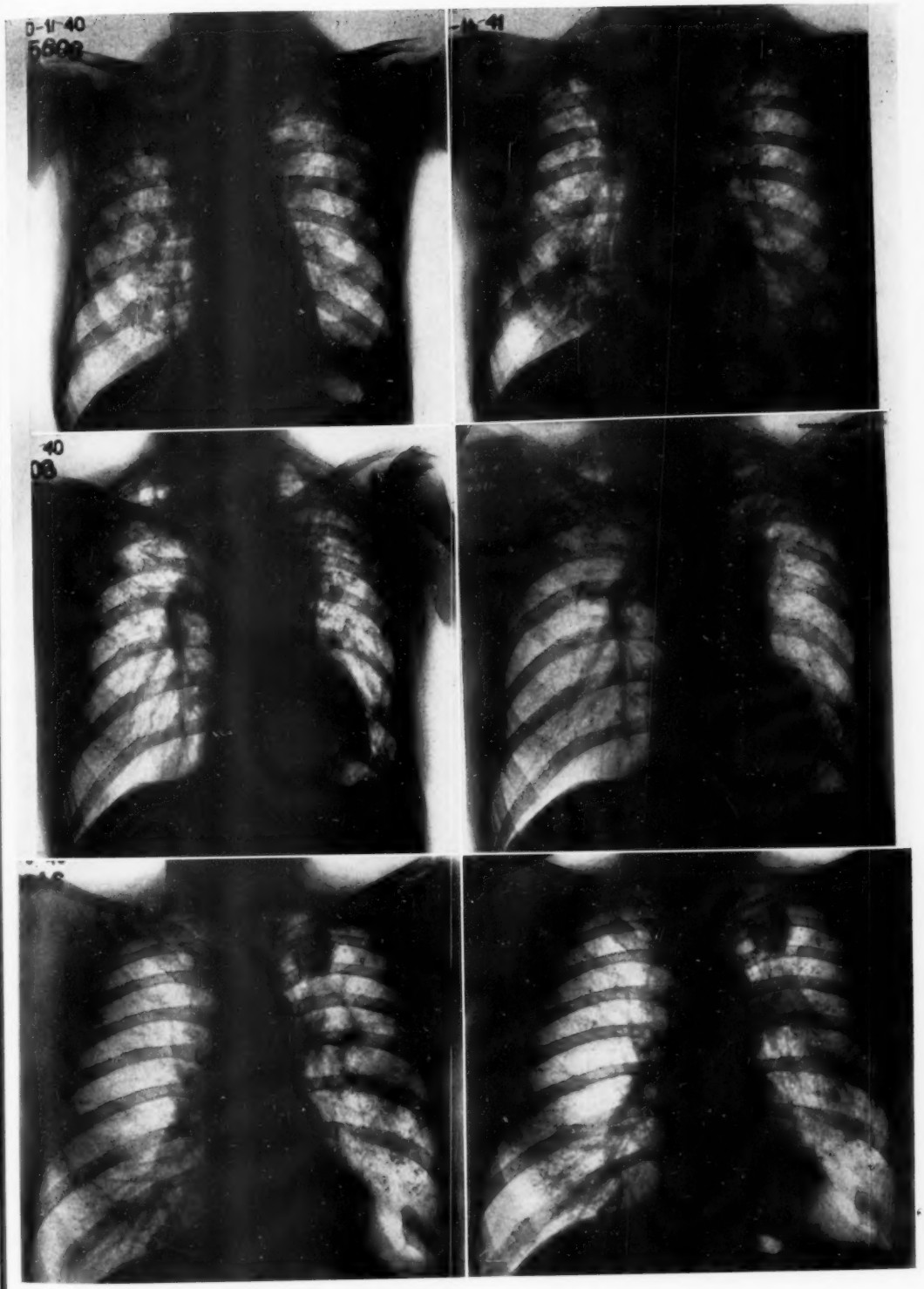
FIG. 2. Case 1. Upper right. Eleven months after starting the diet. Disappearance of the cavities. Fibrosis of the upper lobes. Clearing of the infiltrations below.

FIG. 3. Case 2. Center left. Before diet. Tuberculous involvement of most of the left lung. Several small cavities in the left upper lobe. Infiltrations in the right upper lobe.

FIG. 4. Case 2. Center right. Eleven months after starting the diet. Fibrosis of the upper lobes. Clearing of the infiltrations below. The large rarefaction (bleb) in the right subapical region is unchanged.

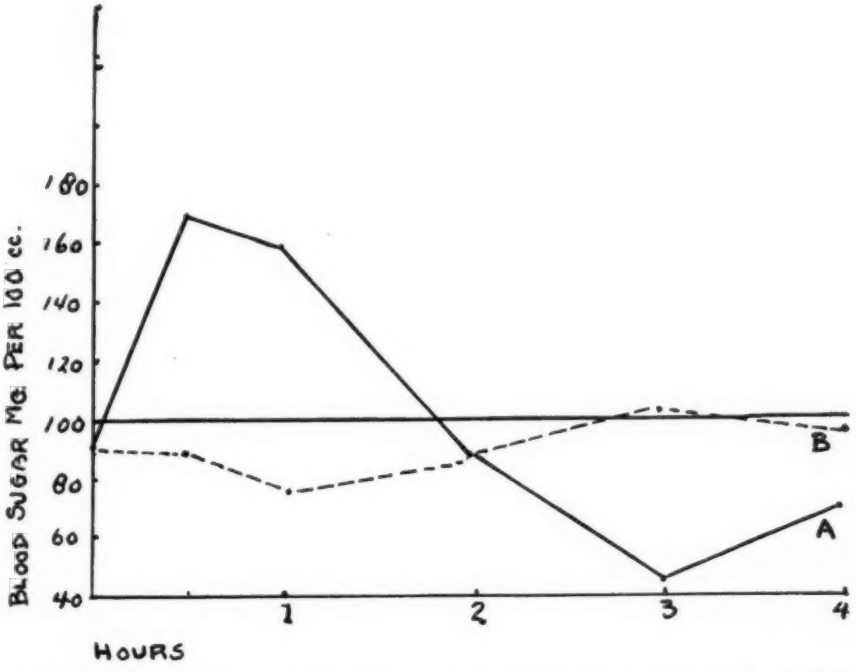
FIG. 5. Case 7. Lower left. Before diet. Three large cavities are present in the left lung. The subapical cavity is filled with inspissated secretion.

FIG. 6. Case 7. Lower right. Four months after starting the diet. The perihilar cavity now appears as a dense shadow. The lowermost cavity cannot be seen.



Comment: An interesting feature in this case was the marked improvement on the low carbohydrate diet in spite of the fact that the glucose tolerance curve showed no definite abnormality. Also of interest was the increase in well-being and strength within the first weeks, long before there was any change in the pulmonary status.

Case 2: B. S., white male, age forty-nine, storekeeper, had a chronic cough for many years. A diagnosis of pulmonary tuberculosis was made in the summer of 1940. He was



GRAPH 3. Case 2. Curve A shows course of the blood sugar after 100 g. of glucose; curve B shows course after low carbohydrate test meal. (Low carbohydrate test meal is the usual breakfast given patients on the low carbohydrate diet. This meal consists of one orange, two eggs, two small soda crackers, one pat butter, a slice of American cheese, cup of milk (C 21 g., P 27 g., F 41 g.).) Patient had marked weakness when blood sugar reached 45 mg. three hours after taking the glucose. The blood sugar shows stabilization after the low carbohydrate meal.

admitted to a hospital where a pocketed tuberculous effusion was aspirated several times with resultant absorption. He was transferred to Montefiore Hospital on September 2, 1940, with a progressive far advanced bilateral tuberculosis with a poor prognosis. On admission he was placed on bed-rest and custodial care. He was dyspnoeic on mild exertion. Examination revealed involvement of most of the left lung with several small cavities in the upper lobe. The upper half of the right lung was infiltrated and in the apex was a large rarefaction. A chest film taken on December 11, 1940 showed some clearing in the lower halves of both lungs (figure 3). However, there was no comparable clinical improvement. He had anorexia, weakness, fatigability and marked pallor. He had

gained 20 pounds, but there was no increase in strength. He had much pain in the left chest and shoulder. The sputum reached about 20 g. daily and was consistently positive for tubercle bacilli.

On December 15, 1940, he was put on the low carbohydrate diet. Two weeks later he went home on a pass and reported that he was not as tired as he had been on a similar occasion one month previously. There was improvement in facial color and diminution in cough and expectoration. His appetite improved. At the end of six weeks, after an initial loss of 5 pounds, he began to gain in weight. By the middle of March, 1941, the chest and shoulder pain had practically disappeared. He was in good spirits and inquired about going home. A chest film in July showed increased fibrosis of the left upper lobe. In October the general condition was considered good enough to warrant pneumothorax therapy on the left. Effective collapse could not be attained and the treatment was promptly abandoned. Clinical improvement continued. On November 17 the sputum was negative for tubercle bacilli. Roentgen examination showed further fibrosis and healing on the left. The large rarefaction on the right showed no change suggesting that this represented a bleb and not a tuberculous cavity (figure 4).

The patient was discharged on December 16, 1941. During the last four weeks in the hospital four consecutive smears of the sputum, including three concentrates, were negative for tubercle bacilli. One examination of the gastric contents was also negative for tubercle bacilli.

Comment: With bed-rest and on a high carbohydrate diet this patient gained 20 pounds, showed some clearing on X-ray examination, without, however, any parallel symptomatic improvement. He was weak and dyspnoeic. With the change to a low carbohydrate diet, there was an initial loss of 5 pounds, with, however, an increase in strength and general clinical improvement and apparent conversion of his sputum.

Case 3: E. O., white male, thirty-eight years, married, was admitted to the Montefiore Hospital in July, 1936. His illness began in the winter of 1935 with a cold, followed by persistent cough, expectoration, anorexia, sweats, loss of weight and weakness. In June, 1936, a diagnosis of pulmonary tuberculosis was made at another hospital and a left pneumothorax was induced. He was transferred to Montefiore Hospital in July. X-ray examination revealed left pneumothorax with uncollapsed cavities and some spread to the right lung. The sputum was positive for tubercle bacilli. The blood Wassermann and Kahn tests were 4-plus. The spinal fluid was negative. Antiluetic therapy was begun. Pneumothorax was discontinued in November, 1936, because of persistent positive sputum and uncollapsed cavities. A first-stage thoracoplasty was done on February 18, 1937. The sputum continued positive and there was spread to the left lower lobe. On May 10, 1937, a second stage thoracoplasty was done. During the next eleven months the sputum continued positive and there was some spread of the disease to the left lower lobe. He was transferred to the Montefiore Country Sanatorium on May 6, 1938, where he remained until October 9, 1938. He became worse at the Sanatorium. He became febrile, felt weaker and had several haemoptyses. He had much pain at the thoracoplasty wound which was worse on inspiration and for which a left phrenicectomy was done in August without relief. He returned to Montefiore Hospital in October. X-ray examination showed a clear right lung and no cavity visible on the left. The sputum was still positive. Bronchoscopy in December was negative for lesions in the bronchi and larynx. All during 1939 he continued to streak, was weak, bed-ridden and had so much pain in the left chest

that paravertebral block was considered. X-ray examination on April 13, 1939, showed good collapse on the left with no visible cavity and a clear right lung. The sputum continued positive. In spite of this objective improvement his subjective symptoms continued. He was unable to eat any breakfast. Whenever he attempted to eat breakfast he would vomit soon after. There was no change in his condition during 1940. He had daily attacks of flushing and sweating. He was mentally depressed and feared he would never leave the hospital. In November, 1940, the sputum became negative for the first time and remained so thereafter until his discharge in September, 1941. Two attempts to get him out of bed were unsuccessful because of extreme weakness and dyspnoea.

On February 1, 1941, he was put on the special diet. At this time he was streaking at weekly intervals, sometimes oftener. He expectorated about two cups of sputum daily. He was completely bed-ridden. He was unable to sit up and take his meals. Sitting up to write two paragraphs of a letter tired him out. He was unable to eat any breakfast, a condition which had persisted since the onset of his illness in 1936. A glucose tolerance test showed the flat hypoglycaemic type of curve. An X-ray film at this time showed good collapse on the left with no visible cavity and a clear right lung just as did the X-ray film taken in April, 1939.

After three weeks on the diet there was noticeable improvement. Blood was seen in the sputum less often and in smaller amounts. He was able to eat some breakfast for the first time in four years. He could sit up to eat without support for the first time in a year and could write four pages of a letter without getting tired.

After four weeks he reported a brighter mental outlook. On March 14 he was able to eat a full breakfast. He was able to get out of bed and sit up in a wheel chair for several minutes without much fatigue. He was no longer having flushes and sweats. On March 23 he sat up in a chair two times, each time for thirty minutes. He was also able to stand unsupported. After ten weeks the sputum, which had always been thick, green-yellow and purulent, was thinner, frothier and less foul. The cough was about the same. The severe pains in the left chest were no longer present. On May 12 he was able to walk with a cane for ten minutes. Improvement continued steadily in all respects. In August he was able to attend a ball-game. Streaking had virtually disappeared. The sputum was half of what it formerly was. He had mild dyspnoea after walking for some time. He was discharged on September 25, 1941. An X-ray film of the chest at this time revealed no change when compared with the films taken before the diet was started. Since discharge from the hospital he has been attending the follow-up clinic and reports steady improvement. His only symptom is slight dyspnoea on exertion. He had gained only 4 pounds during seven months on the diet. The sputum had always been negative for tubercle bacilli during these seven months.

Comment: This patient's response to the change in diet suggests that his symptoms and disability were due to the disturbance in carbohydrate metabolism, and specifically to the high carbohydrate ward diet with its depressant effect on blood sugar levels. He had no signs of active disease since November, 1940, and everything pointed to healing. The sputum had been negative since November, 1940. X-ray films of the chest taken at the time of discharge showed no change when compared with films taken in April, 1939 and February, 1941.

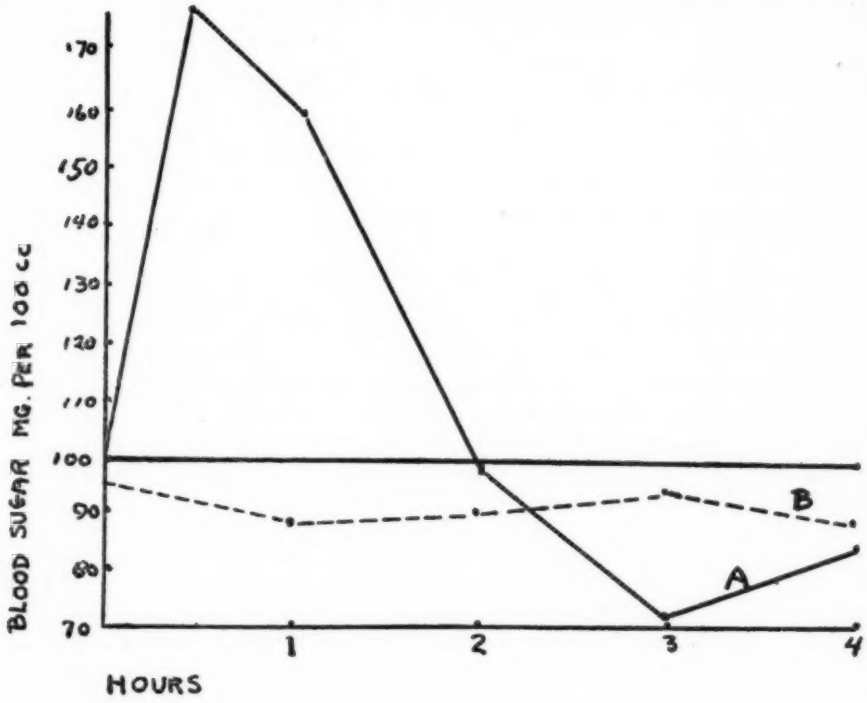
Case 4: J. M., white male, thirty-seven years, married, born in France, was admitted to Montefiore Hospital on September 16, 1940, with advanced bilateral pulmonary tubercu-

losis. In 1933 and 1935 he had attacks of pain in the left chest diagnosed as pleurisy. In March, 1939, he was treated for a duodenal ulcer. Late in 1939 he began to cough frequently, expectorate and complain of easy fatigue. He went to Florida in January, 1940, for a rest. An X-ray examination of the chest showed extensive tuberculosis and he was admitted to a sanatorium. A film revealed bilateral infiltrations and a large cavity in the left upper lobe. On January 20, 1940, a left pneumothorax was induced. This was followed by some subjective improvement. In May the sputum was still positive. On May 7, 1940, a left pneumonolysis was performed. This was followed shortly by a pleural effusion. He returned to New York and was admitted to Montefiore Hospital on September 16. An X-ray examination at this time revealed a partly collapsed left lung with fluid at the base, scattered infiltrations in all lobes on the right with small cavities in the right upper. Aspiration of the left chest yielded thick greenish-yellow pus. Spreads and cultures of the pus revealed no tubercle bacilli or other pathogens. The sputum was positive for tubercle bacilli. The blood Wassermann and Kahn tests were 4-plus. He received frequent aspirations and irrigations of the chest. The pus was flaky, thick and often plugged the needle. Antiluetic therapy was also begun.

On December 30, 1940, just before being put on a low carbohydrate diet, his status was as follows: weight 145 lbs., facial pallor, moderate cough and about 25 g. of purulent sputum daily. He had frequent headaches before meals and epigastric discomfort and fulness after meals. He spent most of the time in bed, complained of heaviness over the chest and shortness of breath on moderate exertion. He was often depressed mentally. X-ray examination of the chest revealed a collapsed left lung with fluid at the base, and generalized infiltration on the right with small cavities in the upper lobe. The pus from the left chest was still thick, greenish-yellow.

After three weeks there was a distinct improvement in his appearance. His cheeks showed some color and he appeared brighter. He said he felt more buoyant and hopeful. He felt stronger and had more "pep." His headaches and dyspeptic symptoms had almost completely disappeared. His appetite improved. He had less heaviness over the chest and less dyspnoea on exertion. He had lost 4 pounds. The sputum became negative at this time. During January and February his chest was aspirated less often. The fluid became thinner, less cloudy and accumulated in smaller amounts. On March 25, 1941, the fluid was described as thin, amber and clear. On April 16, X-ray examination of the chest revealed some expansion of the left lung. Fluid was still present at the base. He continued symptom-free. His appetite was very good. He was up and about and had no heaviness over the chest or dyspnoea on exertion. He appeared buoyant, hopeful and showed more interest in his neighbours. Expectoration amounted to 5 to 10 g. daily. By May his weight returned to 145 pounds. The chest fluid was clear and watery. He felt strong, and could walk up a flight of stairs without fatigue or dyspnoea. The sputum continued negative. He was transferred to the Montefiore County Sanatorium for further convalescence on June 17. There were no facilities for keeping him on the low carbohydrate diet. However, he avoided carbohydrate-rich foods as much as possible. He took no sugar, ate about one-half slice of bread with his meals and took little of cereals, potatoes and desserts. He did have attacks of pain and vomiting which could have been attributed to these foods although they were taken in small quantities. The left lung showed gradual reëxpansion and the right lung showed clearing. No chest aspirations were performed. On December 20, 1941, his weight was 157 pounds. He was practically asymptomatic with minimal amount of negative sputum. X-ray examination showed the left lung to be about 90 per cent reëxpanded with no evidence of cavitation. Healing was evident by fibrosis. The right lung showed marked clearing.

Comment: This patient had considerable relief from digestive symptoms within a few days after going on the diet. This improvement could not have been due to any change in the pulmonary status. It suggests that these symptoms are due to the disturbance in carbohydrate metabolism, in particular to the wide fluctuations in blood sugar levels (graph 4). While the antiluetic therapy, aspiration and irrigation of the empyema cavity undoubtedly contributed to his general recovery, it was felt that these measures could not have



GRAPH 4. Case 4. Curve A after 100 g. glucose; curve B after low carbohydrate meal. Note wide fluctuations in blood sugar after glucose with fall to mild hypoglycaemia in the third hour. This patient had dyspeptic symptoms two to three hours after meals.

effected so rapid a recovery. The usual course of pyopneumothorax with cavitation is more protracted.

Case 5: H. P., white male, age fifty-seven, was found to have pulmonary tuberculosis in April, 1937. A right pneumothorax was induced in July, 1937. This was soon followed by a sterile effusion and obliterative pleuritis, forcing discontinuation of the treatment. In September, 1939, a small apical cavity appeared in the left lung. Attempted induction of left pneumothorax was unsuccessful. He was admitted to Montefiore Hospital in December, 1940, with extensive bilateral pulmonary disease. A chest film showed a shrunken right upper lobe and several small cavities in the left upper lobe. Cough was moderate and expectoration was scant, covering only the bottom of the cup in twenty-four hours. The sputum was positive for tubercle bacilli. He had frequent severe heartburn associ-

ated with soreness under the right breast. The heartburn was sometimes accompanied by vomiting. His weight which was 158 pounds on admission increased to 164 pounds in February, 1941.

He was put on the low carbohydrate diet on February 24, 1941. Soon after the heartburn disappeared and his appetite improved. He stopped vomiting. The pain in the right breast, a constant source of complaint for many months, was no longer present. During the first month on the diet he lost 6 pounds, but felt stronger. Subjective improvement continued until the date of discharge, June 19, 1941. A chest film showed no change in pulmonary status. The sputum was positive for tubercle bacilli. Since discharge, the patient, despite a keen desire to continue the dietary regimen, has been forced, because of financial difficulties, to follow a diet consisting mainly of carbohydrate-rich foods. His breakfast, for example, consists of two rolls and coffee. As a result, after six months, he has lost 20 pounds. His heartburn has returned. Although the chest film shows no progression, his general condition is definitely worse.

Comment: The relief from heartburn and weakness shortly after going on the diet, without any change in his pulmonary status, suggests that his symptoms were due to the disturbance in carbohydrate metabolism. This is substantiated by the prompt return of these symptoms when he was forced to eat carbohydrate-rich foods.

Case 6: A. N., white male, age twenty-four, a clerk, was admitted to the Montefiore Country Sanatorium in December, 1938. Pulmonary tuberculosis was first discovered in September, 1938. Examination revealed exudative disease with cavitation involving the upper third of both lungs. Left pneumothorax was induced in March, 1939, and abandoned as ineffective nine months later. This was followed by a tuberculous empyema which responded well to treatment. Pneumothorax was induced on the right in July, 1940. Sputum concentrates were positive for tubercle bacilli. While in the sanatorium the patient failed to improve. He had occasional periods of low-grade fever. He developed an ischio-rectal abscess. He remained pale and underweight. He lost 5 pounds during March, April and May of 1941. It was felt that a thoracoplasty was urgently needed to effect closure of the large cavity in the left upper lobe; however, because of his poor condition, the operation had to be delayed.

On June 17, 1941, he was transferred to the Montefiore Hospital. The opinion at this time was that his condition was as good as it ever would be without surgery and that thoracoplasty should be done. Since the disease in the right lung had not shown any recent roentgenological evidence of progression, it was felt that reëxpansion could be allowed with a fair margin of safety. At the time of admission to the hospital he was pale and thin. He weighed 134 pounds. He was nervous, and occasionally got "worked up in a way that he could not explain." His appetite was poor. Cough was productive of 25 g. of thick green sputum daily. There was a small amount of drainage from the ischio-rectal sinus.

He was put on the low carbohydrate diet on June 26, 1941. On July 2 it was noted that his appetite was much better. After a few weeks he felt stronger. He became more relaxed and no longer complained of nervous spells. In September there was little cough and the sputum had decreased to 10 g. daily. After three months on the diet he had gained 11 pounds. The rectal sinus discharged only a drop of pus in twenty-four hours. In October he was a far better surgical risk than he had been in June. A first-stage thoracoplasty was done on the left on October 21, and a second stage on November 14.

These operations were tolerated extremely well. He was discharged to the Country Sanatorium on December 14. The sputum was still positive for tubercle bacilli.

Comment: This patient was admitted to the sanatorium and was kept there in order to build him up for surgery. However, his course was progressively downhill. He was transferred to Montefiore Hospital because he was too ill to remain at the sanatorium. There was a prompt and sustained response to the change in diet. He became an excellent surgical risk and withstood the two operations with a minimum of discomfort.

Case 7: H. C., white male, age forty-nine, first came under observation for pulmonary tuberculosis in August, 1928. Roentgen examination showed infiltrations throughout the left lung, a large cavity in the left upper lobe and scattered infiltrations in the right lung. The sputum was positive for tubercle bacilli. The clinical course at that time was quiescent. In the ensuing years the patient had frequent admissions to Montefiore Hospital with slow progressive involvement of the left lung. In 1934 the left subapical cavity was replaced by a dense homogeneous shadow, apparently caused by filling with inspissated secretions. A large fresh cavity appeared in the left hilar region. Bronchoscopic study revealed a stenosis of the left upper lobe bronchus. Artificial pneumothorax was induced in 1935 on the left but discontinued as ineffective. In November, 1935, there were several haemoptyses. A large haemoptysis occurred in July, 1938, and several more in 1939. Early in 1940 there was a massive spread on the left with excavation in the left mid-lung zone below the hilar cavity. Treatment consisted of bed-rest and symptomatic care.

On February 26, 1941, he was put on the low carbohydrate diet. His chief complaints at this time were almost daily streaking, pain in the left chest and shoulder and dyspnoea on mild exertion. There was frequent cough and wheezing. The sputum was purulent, reached 100 to 175 g. daily and was positive for tubercle bacilli. His appetite was poor. A chest film showed the old subapical homogeneous shadow, as well as the large perihilar and mid-zone cavities (figure 5). These two latter cavities had shown some slight reduction in size during 1940. After two weeks on the diet, streaking ceased and never recurred. Cough and pain in the chest and shoulder diminished. After four weeks he was able to walk about with less dyspnoea. A chest film on April 19 showed the perihilar cavity to be smaller and appearing as a dense shadow. The mid-zone cavity was also much smaller. At the end of May, three months after starting the diet, he had minimal cough and the sputum was reduced by one-half. Although he had lost 10 pounds, he felt much stronger. At the end of June he began to regain weight. A chest film on June 26 showed the perihilar dense shadow reduced in size. The mid-zone cavity could not be seen (figure 6). In July the sputum was occasionally negative for tubercle bacilli. The weight had come up to the pre-diet level. On August 19, 1941, after six months on the diet, he was discharged improved. There had been no streaking for five and a half months. When last seen in January, 1942, five months after discharge, he said he had streaked but once. He was still on the diet and was virtually symptom-free.

Comment: This patient also had an initial loss of 10 pounds during the first two months on the diet. There was, however, an increase in strength and general clinical improvement. This suggests that the change in weight was due to the loss of substances not essential to health and strength. Striking in this case was the prompt and sustained cessation in streaking in view of the long history

of streaking and haemoptyses. Also striking was the disappearance of the large cavity in the mid-zone after four months on the diet.

THE DIET

The diet employed ranged from 2,309 to 2,920 calories (carbohydrate, 114 to 124 g.; protein, 101 to 129 g.; fat, 161 to 212 g.). This was divided into three regular meals with feedings between meals (10 a.m. and 3 p.m.) and at bedtime of a milk and cream mixture. Six thin soda crackers were allowed each day, two with each meal. Excepting the soda crackers, the carbohydrate content of the diet was ingested in the form of 5 and 10 per cent vegetables and fruits and dairy products. The following carbohydrate-rich foods were completely avoided: bread, cereals, potatoes, sugar, corn, rice, tapioca, split-peas, noodles, macaroni, spaghetti, cake, candy, ice-cream, pancakes, etc. Soy-bean flour muffins were given from time to time and enjoyed. Breakfast would consist of a 10 per cent fruit, 2 eggs, 2 crackers, butter, cheese and a cup of the milk-cream mixture. Dinner would consist of broth, meat, 5 and 10 per cent vegetables (cooked and and raw), 10 per cent fruit, 2 crackers and milk-cream mixture. Supper would consist of broth, fish, 2 eggs, 5 and 10 per cent vegetables (cooked and raw), 10 per cent fruit, 2 crackers, butter, milk-cream mixture. Patients were encouraged to eat nuts between meals if they were hungry. High carbohydrate nuts, such as peanuts and cashews, were not allowed.

After going on the diet patients usually complain of being hungry after meals. They don't have the satiety that comes with eating foods like bread, cereals and potatoes. For this reason they are encouraged to take some food between meals. After a week or two this hunger disappears and the desire for carbohydrate-rich foods usually subsides. Some patients interpret this hunger after meals as an indication of insufficient nourishment. It is necessary to tell them that they are getting sufficient nourishment in spite of the feeling of hunger. Underweight patients may show a loss in weight during the first few weeks on the diet. One may reassure such patients by telling them that such loss is not harmful and that they will eventually gain in weight. The fact that patients gain in strength and improve otherwise in spite of the loss in weight is usually reassuring.

Practically all the patients had to be encouraged at the beginning of the treatment. Sensing the experimental nature of the diet they were reluctant to give up foods they always enjoyed eating. They were skeptical when told that bread and cereals were preventing their recovery. After a few weeks, however, when they began to feel stronger, appear healthier, and when they began to lose some of their symptoms, they realized the value of the diet and were glad to continue on it. Three patients refused to continue on the diet after a few weeks because of initial loss in weight and because they were unwilling to be subjects of an experiment. Against the possibility that the beneficial effects of the diet were due to the psychological effects of a new form of therapy it can be said that the patients were uniformly antagonistic towards the diet at the outset. Further, any beneficial effects resulting from a new form of therapy are not to be

observed in all patients and are not lasting. All of our patients responded favorably and the improvement was progressive and permanent as long as they continued on the diet. Prompt exacerbation of symptoms was reported by one of the patients when he left the hospital and, because he was unable to purchase the more expensive proteins and fats, went back to a high carbohydrate diet (case 5). Prompt return of digestive symptoms was observed in another patient who ate small quantities of carbohydrate-rich foods when he left the hospital and went to the Country Sanatorium (case 4).

Glucose tolerance tests were done on 9 patients in the group. Three had hypoglycaemic curves, 3 hyperglycaemic curves and 3 had curves with values within normal limits. On low carbohydrate diets patients with hypoglycaemia showed elevation of blood sugar levels to normal values; patients with hyperglycaemia showed reduction of blood sugar levels to normal or near normal values. Since the patients with normal curves responded to the change in diet, it is evident that some abnormality in carbohydrate metabolism was being overcome which could not be elicited with the glucose tolerance test. As has been suggested, on a low carbohydrate diet, there is no suppression of output from the liver of endogenous glucose which is believed to be the more readily oxidized γ-glucose. On a high carbohydrate diet the organism oxidizes less glucose because of the suppression of output of endogenous glucose, and during this suppression there will be available the less reactive α-β-glucose.

In our group of 10 patients 7 had gain in weight ranging from 5 to 25 pounds. One of these had an initial loss of 4 pounds during the first three weeks. One patient lost weight without regaining any. The loss was 5 pounds. One patient, whose weight was normal for his height, had no change at all. Another patient who lost 10 pounds during the first three months subsequently gained them back.

Patients who lose weight usually do so during the first weeks. The weight then becomes stabilized and either remains constant or shows a rise. In spite of loss in weight there is an increase in strength and general clinical improvement. This is in contrast to frequent gain in weight in patients with pulmonary tuberculosis without increase in strength and without clinical improvement on high carbohydrate ward diets. The early and rapid loss in weight suggests that it is due to loss of water chiefly. The withdrawal of carbohydrate-rich foods apparently exerts a dehydrating effect. Gain in weight on carbohydrate-rich diets, without clinical improvement and often with progression of the disease, suggests that the gain is due chiefly to the storage of water and fat—of doubtful value to the patient.

Patients may show improvement on the diet in a short time. There is usually an improvement in appetite. Patients who had little or no desire for food soon enjoyed their meals. Case 3, who had been unable to eat any breakfast for about four years, was able to do so after several weeks. Case 7, who had had no appetite ever since the onset of his illness, had prompt return of appetite after two weeks. Such patients have no difficulty in following the diet. Common digestive complaints such as fulness after meals, belching, heartburn, flatulence,

epigastric heaviness and abdominal cramps, disappear after a few days. Patients were surprised to learn that foods like cereals and baked potatoes, generally regarded as "light" and easily digested, were responsible for their post-prandial distress. They were also surprised to learn that meat and fish could be eaten often and in liberal quantities without digestive disturbances. This early relief from gastrointestinal symptoms, long before there could be any appreciable change in the pulmonary status, suggests that they are not "reflex" from the infection or due directly to the infection, but are due rather to some readily reversible mechanism brought about by the change in diet. Investigation suggests that these symptoms arise from the disturbance in carbohydrate metabolism which interferes with gastrointestinal motility and secretion of digestive juices. The cells of the gastrointestinal tract utilize glucose for energy purposes and may suffer dysfunction when there is subnormal oxidation of glucose. The fact that exactly similar gastrointestinal symptoms in patients without tuberculosis or other infections respond to a similar change in diet is further evidence that they are not due directly to the infection. The possible mechanism for these symptoms has been discussed more fully in other communications (29, 30).

Relief from precordial symptoms in the form of pain, heaviness over the chest, palpitation and dyspnoea, both at rest and on exertion, was also obtained in all patients after varying periods of time. Pain in the right or left shoulder, often attributed to arthritis, bursitis, or regarded as referred cardiac pain, disappeared in 2 patients after several weeks. The cardiac symptoms apparently arise from the partial deprivation of the heart muscle of its most important source of energy, glucose. The mechanism for the production of these symptoms has been discussed in another communication (31).

Respiratory symptoms, such as cough, wheezing, difficulty in raising sputum, were either completely relieved or greatly ameliorated. The sputum in all but 2 patients fell gradually in amount as the patient improved. In all patients with thick purulent sputum, there was a gradual change to a frothy watery sputum. This change in character readily explains the greater ease in expectoration.

Striking also was the improvement in the mental state of the patients. They appeared more buoyant and hopeful. They were less subject to periods of depression. The eyes became brighter, the face more relaxed and fuller. Pallor and pastiness were replaced by a healthier color. Patients became less introspective and less anxious about their illness. They became more sociable and less irritable. Of course, much of this improvement could be attributed to healing of the pulmonary lesions and reduction in toxaemia. However, we have observed similar psychic changes in patients with hypoglycaemia and hyperglycaemia who had no tuberculosis. For this reason we have come to the conclusion that the improvement in the psychological condition is due to the improvement in glucose utilization brought about by the change in diet. There is a report in the literature of improvement in psychotic patients with hyperglycaemia who were treated with diet and insulin (32). When one considers that glucose is the chief source of energy for the brain and that neurons utilize

oxygen in proportion as they utilize glucose, it is evident that the neurological and mental symptoms are possibly due to a cellular asphyxia. Symptoms arising from asphyxia from any cause are exactly similar to those arising from reduced glucose oxidation. Of course the tuberculous infection may aggravate or precipitate mental and neurological symptoms by aggravating the disturbance in carbohydrate metabolism, just as an infection or toxaemia will aggravate the disturbance in carbohydrate metabolism in a diabetic.

Since it was thought that the amount of glycogen stored in the liver might be fundamentally related to persistence of the tuberculous infection, an attempt was made to get some indirect information, by means of the respiratory quotient, on the liver glycogen stores of our patients before and after they were put on the low carbohydrate diet. The fasting RQ was calculated from samples of respired air collected for fifteen minutes. An RQ below 0.8 would indicate subnormal oxidation of glucose resulting from subnormal liver glycogen stores. An RQ between 0.8 and unity would indicate normal glucose oxidation. If a patient had a low RQ before going on the diet and a normal RQ after going on the diet, it would indicate an increase in glucose oxidation due to an increase in glycogen stores brought about, paradoxically, by the low carbohydrate diet. The RQ values, however, in our patients varied greatly and did not permit us to draw any conclusions.

Because of the clinical improvement noted in our patients on the low carbohydrate diet, there is a strong possibility that there was a concomitant increase in liver glycogen stores. It is well known that improvement in diabetes is associated with an increase in glycogen stores on restricted carbohydrate diets, with or without insulin. It is very likely that improvement in patients with hypoglycaemia may also be accompanied by an increase in glycogen stores, even on a low carbohydrate intake. There is experimental evidence that a so-called balanced diet with fairly high intake of carbohydrate-rich foods need not bring about normal liver glycogen storage, but, in fact, may produce a fatty liver. Spellberg and Keeton (33) produced liver changes in guinea pigs and rabbits with diets containing an abundance of carbohydrates in the form of oats, wheat bran and dextrose. They state, "The development of liver changes in an animal receiving an 'adequate' diet leaves one to wonder whether our conception of such a diet is not an erroneous one." They believed that some factor was absent in the diet which caused fatty changes. It has been our impression for some time that the continued ingestion of carbohydrate foods may prevent normal liver glycogen storage. From clinical observations we have concluded that a diet rich in protein and which avoids carbohydrate-rich foods can better bring about normal glycogen stores, especially in the presence of infection. On such a diet carbohydrate is ingested in the form of 5 and 10 per cent vegetables and fruits.

We have stressed in this communication that the low carbohydrate diet is effective because it increases glucose-oxygen consumption in the entire organism. We believe that the fundamental factor responsible for susceptibility to, and persistence of the tuberculous infection, namely, a reduced glucose-oxygen consumption, is thereby overcome. Apparently a normal carbohydrate metabolism

is the essential and fundamental mechanism upon which other defense mechanisms depend. This is true not only for the diabetic but for the non-diabetic as well. The normal combustion of glucose supplies the energy for chemical reactions needed for the production of tissue and humoral immunological substances. In addition, the high protein intake makes available chemical substances more suitable for tissue repair.

SUMMARY

On the assumption that carbohydrate-rich foods exert a depressant effect on oxygen consumption with resultant lowering of the organism's ability to overcome infection, 10 patients with advanced pulmonary tuberculosis suitable only for custodial care were put on a low carbohydrate diet. All 10 patients responded to the diet as evidenced by gain in strength, general clinical improvement, healing of cavities and clearing of infiltrations. Five patients have returned to their homes; 2 patients were gotten into shape for surgery; the other 3 are still in the hospital and improving steadily. The beneficial effects on the diet are attributed to increased glucose-oxygen consumption. This is brought about by elevating the blood sugar to normal levels in patients with hypoglycaemia; by restricting carbohydrate-rich foods in patients with hyperglycaemia; and by making available the more highly reactive γ-glucose in patients who showed neither hypoglycaemia nor hyperglycaemia. The evidence for the existence of γ-glucose is presented.

It is believed that a low carbohydrate, high protein diet can bring about normal liver glycogen storage. Such storage is necessary for adequate delivery of endogenous glucose to tissues so that cellular oxidations may be maintained at optimum level.

The early and sustained relief from digestive, cardiac, respiratory, nervous and mental symptoms suggests that such symptoms are due directly to the disturbance in carbohydrate metabolism and abnormal blood sugar levels.

This investigation also affords clues to the efficacy of physical and mental rest and good nutrition in the treatment of tuberculosis.

SUMARIO

Suponiendo que los alimentos ricos en hidratos de carbono ejercen un efecto depresor sobre el consumo de oxígeno con la resultante baja de la capacidad orgánica para vencer la infección, impúsose un régimen bajo en hidratos de carbono a 10 enfermos de tuberculosis pulmonar avanzada y apropiada solamente para asistencia institucional. Los 10 enfermos respondieron al régimen, según demostró el aumento de fuerzas, la mejoría clínica general, la cicatrización de las cavernas, y la desaparición de las infiltraciones. Cinco enfermos regresaron a sus hogares; 2 fueron preparados así para la cirugía, y los otros 3 continúan en el hospital y mejoran constantemente. El efecto beneficioso de esta dieta se imputa al aumento en el consumo de glucosa-oxígeno, lo cual se obtiene elevando la glucemia a cifras normales en los hipoglucémicos, limitando los alimentos ricos en hidratos de carbono en los hiperglucémicos, y poniendo la

γ-glucosa más reactora, a la disposición de los enfermos que no revelaron ni hipo- ni hiperglucemia. Preséntanse pruebas de la existencia de γ-glucosa.

Para los autores, una alimentación baja en hidratos de carbono y rica en proteína puede obtener una fijación normal de glucógeno en el hígado, lo cual se necesita para una entrega adecuada de glucosa endógena a los tejidos, a fin de poder mantener la oxidación celular a su tenor óptimo.

El alivio temprano y sostenido de los síntomas digestivos, cardíacos, respiratorios, nerviosos y mentales indica que se deben directamente al trastorno del metabolismo hidrocarbonado y a las cifras glucémicas anormales.

Esta investigación también ofrece indicaciones de la eficacia del reposo físico y mental, y de la buena nutrición en el tratamiento de la tuberculosis.

REFERENCES

(1) Faber, Knud: Tuberculosis and nutrition, Acta tuberc. Scandinav., 1938, *12*, 287.
(2) Weigert: Cited by Adlersberg and Porges (3).
(3) Adlersberg, D., and Porges, O.: Uber Die Entwassende Wirkung Kohlehydratarmer Kost und Ihre Therapeutische Verwendbarkeit, Klin. Wchnschr., 1933, *12*, 1446.
(4) McCullagh, E. P., and Johnston, C. R. K.: Manipulation of glucose tolerance by diet, Am. J. M. Sc., 1938, *195*, 773.
(5) Paton, J. H. P.: Relation of excessive carbohydrate ingestion to catarrhs and other diseases, Brit. M. J., 1933, *1*, 738.
(6) Spiesman, I. G., and Arnold, Lloyd: Host susceptibility to common colds, Am. J. Digest Dis. & Nutrition, 1937, *4*, 438.
(7) Cited by Paton.
(8) Dameshek, Wm., Myerson, A., and Stephenson, C.: Insulin hypoglycemia, Arch. Neurol. & Psychiat., 1935, *33*, 1.
(9) Himwich, H. E., and Fazekas, J. F.: The effect of hypoglycemia on the metabolism of the brain, Endocrinology, 1937, *21*, 800.
(10) Holmes, E. G.: Oxidations in central and peripheral nervous tissues, Biochem. J., 1930, *24*, 914.
(11) Dickens, F., and Greville, G. D.: Metabolism of normal and tumor tissue, Ibid., 1933, *27*, 832.
(12) Wortis, S. B.: Respiratory metabolism of excised brain tissue, Am. J. Psychiat., 1934, *90*, 725.
(13) Cannon, W. B., McIver, M. A., and Bliss, S. W.: Studies on the conditions of the activity in endocrine glands, XIII. A sympathetic and adrenal mechanism for mobilizing sugar in hypoglycemia, Am. J. Physiol., 1934, *69*, 46.
(14) Richardson, Russell: Immunity in diabetes, II. Relative importance of nutritional state and of blood sugar level in influencing development of the agglutinin titre after typhoid vaccine, J. Clin. Investigation, 1935, *14*, 389.
(15) Richardson, Russell: Immunity in diabetes, III. Relation of tissue glycogen and blood chemistry to bacterial dissemination, antibody formation and survival after infection in diabetes, Ibid., 1941, *17*, 69.
(16) Sandler, B. P.: The production of neuronal necrosis and injury with the virus of poliomyelitis in rabbits during insulin hypoglycemia, Am. J. Path., 1941, *17*, 69.
(17) Cori, C. F.: Physiol. Rev., 1931, *11*, 143.
(18) Benedict, F. G., and Joslin, E. P.: Metabolism in diabetes mellitus, Carnegie Inst. of Washington Pub. 136, 1910, 230.
(19) Weiss and Rapport: Quoted by Lusk, Science of Nutrition, 4th ed., W. B. Saunders & Co., Philadelphia, 1928, p. 306.
(20) Rubner: Quoted by Lusk, Ibid., p. 308.

(21) Lusk, Graham: Science of Nutrition, 4th ed., W. B. Saunders & Co., Philadelphia, 1928, p. 308.

(22) Hawk, P. B., and Bergeim, O.: Practical Physiological Chemistry, 9th ed., P. Blakiston's Son & Co., Philadelphia, 1927, p. 71.

(23) Shaffer, P. A.: Intermediary metabolism of carbohydrates, Physiol. Rev., 1923, *3*, 394.

(24) Levene, P. A.: Active Glucose, Chem. Rev., 1928, *5*, 1.

(25) Benedict, F. G., and Carpenter. T. M.: Food ingestion and energy transformation with special reference to the stimulating effects of nutrients, Carnegie Inst. of Washington Pub. 261, 1918.

(26) Soskin, S., Essex, H. E., Herrick, J. F., and Mann, F. C.: The mechanism of regulation of the blood sugar by the liver, Am. J. Physiol., 1938, *124*, 558.

(27) Soskin, S., and Allweiss, M. D.: The hypoglycemic phase of the dextrose tolerance curve, Ibid., 1934, *110*, 4.

(28) Kramer, D. W.: Glucose tolerance curves in pulmonary tuberculosis, 100 cases, J. Lab. & Clin. Med., 1933, *18*, 1212.

(29) Sandler, B. P.: The pain mechanism in peptic ulcer and pseudoulcer syndrome, Rev. Gastroenterol., 1940, *7*, 485.

(30) Sandler, B. P.: Chronic abdominal pain due to hypoglycemia, Surgery, 1941, *9*, 331.

(31) Sandler, B. P.: The control of the anginal syndrome with a low carbohydrate diet, M. Ann. District of Columbia, 1941, *10*, 371.

(32) Robinson, G. Wilse, Jr., and Shelton, Prior: Incidence and interpretation of diabetic-like dextrose tolerance curves in nervous and mental patients, J. A. M. A., 1940, *114*, 2279.

(33) Spellberg, M. A., and Keeton, R. W.: The production of fatty and fibrotic livers in guinea pigs and rabbits by seemingly adequate diets, Am. J. M. Sc., 1940, *200*, 688.

RESULTS OF PHRENIC NERVE OPERATIONS[1]

A Critical Analysis of Fifty-seven Cases from the Surgical Division of the New York District Tuberculosis Hospitals

PAUL L. OWENS[2]

The purposes of this paper are to evaluate the results of operations on the phrenic nerve in the treatment of pulmonary tuberculosis; to determine the type of case in which benefit might be expected after any of the accepted operations.

The problem was approached by the critical analysis of the clinical records of all patients subjected to such operations in the New York State District Tuberculosis Hospitals from the time of their respective openings in 1935 and 1936 to December 31, 1938. A six months period of postoperative observation elapsed before evaluating results.

In these hospitals, a total of 57 cases received operation on the phrenic nerve. Up to and including December 31, 1938, 1,446 persons were admitted who suffered from pulmonary tuberculosis. It will, therefore, be seen that only 3.94 per cent of total admissions received this type of collapse therapy.

During this period of time, 405 patients received therapeutic pneumothorax (with initial failures in 96 instances). One hundred had thoracoplasty in one or more stages and 5 had pleurolytic or plombage operations. Two patients had phrenic operations before completing a month's bed-rest. The remainder were under observation for thirty or more days prior to operation.

The selection of this type of collapse therapy was arrived at by the consensus of staff physicians seated at weekly medical-surgical staff meetings at their respective institutions or at "Consultation Conferences."

A permanent paralysis of the hemidiaphragm was not desired in any of the initial operations and all except one had a simple phrenic crush. In the one exception the phrenic nerve was paralyzed by the injection of 0.1 cc. of ethyl alcohol. No nerves were sectioned, resected or evulsed during the initial stages. When the visceral nerve trunk appeared to be unduly small as it crossed the anterior scalene muscle, a search was made for accessory branches; otherwise the brachial plexus was not dissected.

Of the 57 patients, 7 had two or more operations on the same nerve; 6 had two operations, one had three operations. Four of the 7 (including the patient with three operations) were ultimate failures. Two who had not secured negative sputum after the first operation, did become negative after the second operation and their cavities closed. One whose cavity had closed and whose sputum had become negative after the first operation received a second permanent operation (phrenic resection) to paralyze the hemidiaphragm permanently.

[1] Thesis submitted to the Faculty of the Graduate School of Medicine of the University of Pennsylvania in partial fulfilment of the requirements for the degree of Master of Medical Science (M.Sc. (Med.)) for graduate work in thoracic surgery.

[2] State Tuberculosis Sanatorium, Orlando, Florida.

The final evaluation of the end results was arrived at by an impartial review of the case records six months or more after operation. All cases with the exception of 2 have been traced. Inasmuch as both of these cases had open cavities and positive sputa at the time of last observation, they have been classed as unqualified failures. No cases were classified as successful who received any other from of collapse therapy. No case was considered as successful unless there was roentgenological evidence of cavity closure or fibrotic healing of active diseased areas. The sputum had to be negative not only by direct smear but by concentration for six or more months. An intermittent positive culture in 2 cases has not excluded them from being classed as successful results inasmuch as roentgenological and clinical evidence indicate arrest of disease.

A careful statistical analysis will be made between these successful cases by means of ten tables which show favorable or unfavorable factors which were present in each individual case. In these tables, the groups were considered too small to warrant the figuring of percentage down to decimal fractions.

COMPLICATIONS

Horner's syndrome, caused by cervical sympathetic injury, occurred for a short time in one case. This was only a temporary disturbance and spontaneously disappeared.

Following a recrush of the phrenic nerve the brachial plexus was injured in one instance. Considerable scar tissue was present from the previous operation. A partial paralysis of the muscles innervated by the musculocutaneous nerve persisted for nine months.

Injury to the right recurrent laryngeal nerve resulted in paralysis of right vocal cord in one case. Fortunately, it only persisted for three weeks.

Dyspnoea on exertion occurred in one case. This patient was forty-seven years of age and had considerable fibrosis throughout both lung fields.

An infection of skin and superficial fascia resulted from a secondary operation. This infection cleared up rapidly and caused no ill effects. This was the only wound infection in 65 operations.

Injury to the axillary nerve, in one case, caused a seven months' partial paralysis of the deltoid muscle.

Gastric distress, associated with upper right quadrant pain, occurred postoperatively in one instance.

None of the complications enumerated influenced, in any manner, the final result of the operation.

One patient, upon whom several unsuccessful attempts had been made to institute therapeutic pneumothorax, was having terminal haemorrhages. A phrenic crush performed in the patient's room did not influence the fatal issue.

STATISTICAL ANALYSIS

	Total	*Successful*	
Patients	57	13	23%
Male	22	5	23%
Female	35	8	23%

	Total	Successful	
Left phrenic operation	21	5	24%
Right phrenic operation	36	8	22%
Bilateral phrenic operation	0		
Age of patient			
2nd decade	8	1	12%
3rd decade	25	7	28%
4th decade	17	5	29%
5th decade	3	0	
6th decade	4	0	
Duration of disease			
0–½ year	20	4	20%
½–1 year	13	6	46%
More than 1 year	24	3	12%
Characteristics of disease on operated side			
Minimal	6	2	33%
Moderately advanced	26	6	23%
Far advanced	25	5	20%
Regressive	15	6	40%
Stationary	19	5	26%
Progressive	23	2	8%
Location of disease on operated side			
Upper third of lung	35	8	23%
Upper and middle thirds of lung	7	1	14%
Middle third of lung	13	3	23%
Lower third of lung	2	1	50%

The figures for the lower third or basal lesions are inconclusive because of the few cases.

Roentgenological characteristics			
Infiltration only	7	2	28.5%
Honeycombing	8	2	25.0%
Single cavities	30	8	27.0%
Multiple cavities	12	1	8.0%
Cavity characteristics			
Total cavity cases	42	9	21%
Thin walled	30	8	27%
Thick walled	12	1	8%
Cavities 2 cm. or less	11	3	27%
Cavities more than 2 cm.	31	6	19%
Contralateral side			
Stable	31	10	32%
Quiescent	10	1	10%
Active	16	2	12%

This tabulation demonstrates the unfavorable effect of active disease on the opposite side.

	Total	*Successful*	
Number of operations			
One operation	50	10	20%
Two or more operations	7	3	43%

Table 1 gives a detailed analysis of the thirteen successful cases.

CONCLUSION

Sex of patient or side operated upon for phrenic nerve interruption had no significant effect on the final result.

Patients in the third and fourth decades of life obtained the most benefit.

Duration of disease of less than one year improved the prospect for success.

Cases classified as minimal or moderately advanced have a better chance of receiving aid from this type of collapse therapy.

Dynamic phase of disease is very important, and patients should be chosen who are either regressive or stationary.

The best results were obtained in patients who had the disease in the upper or middle thirds of the lung.

Single cavities having thin walls responded favorably to a phrenic crush provided the cavities were not over 4 cm. in diameter.

If the opposite lung is affected, the disease should be quiet or stable on that side.

With a realization that sex and the diseased side involved are not of significant importance, it would appear from this study that the ideal patient for phrenic nerve operation would be a person in the third or fourth decade of life, with minimal disease of less than one year's duration, located in either the upper or middle thirds of the lung and preferably in the regressive phase. The roentgenograms should disclose infiltration only or at most a single small thin-walled cavity. The opposite side must be stable.

CONCLUSIONES

El sexo del enfermo o el lado operado para obtener la interrupción del frénico no afectó mayor cosa el resultado definitivo.

Los enfermos en el tercero y cuarto decenios de la vida fueron los que obtuvieron más beneficio.

Las probabilidades de éxito aumentaron cuando la enfermedad había durado menos de un año.

Los casos clasificados como mínimos o ligeramente avanzados tienen más probabilidades de beneficiarse con esta forma de colapsoterapia.

La fase dinámica del mal es muy importante, y debe escogerse a enfermos ya regresivos o estacionados.

Obtuviéronse los mejores resultados en los enfermos que tenían la enfermedad en los tercios medios o superiores del pulmón.

Las cavernas aisladas de paredes delgadas respondieron favorablemente a la trituración del frénico con tal que aquéllas no midieran más de 4 cm. de diámetro.

TABLE 1

CASE NUMBER	SEX	AGE	CLASSIFICATION	SIDE	LEVEL	DURATION IN MONTHS	CHARACTER	TOTAL SIZE OF CAVITIES	WALLS	STATUS	OPPOSITE SIDE	NUMBER OF OPERATIONS
I	F	19	Moderately advanced	R	Upper third	2	Multiple cavities	3 x 3	Thick	Progressive	Quiet	1
II	F	21	Moderately advanced	L	Upper third	9	Single cavity	1 x 1	Thin	Stationary	Stable	1
III	F	22	Moderately advanced	R	Upper and middle thirds	11	Honeycomb			Stationary	Stable	1
IV	F	23	Minimal	L	Upper third	3	Infiltration			Progressive	Stable	1
V	F	24	Far advanced	R	Middle third	10	Single cavity	1 x 2	Thin	Stationary	Active	2
VI	F	26	Minimal	R	Lower third	12	Infiltration			Regressive	Stable	1
VII	F	28	Moderately advanced	R	Upper third	4	Single cavity	2 x 2	Thin	Stationary	Stable	1
VIII	M	29	Moderately advanced	R	Middle third	12	Single cavity	3 x 3.5	Thin	Regressive	Active	1
IX	M	31	Far advanced	L	Upper third	90	Single cavity	2 x 4	Thin	Regressive	Stable	1
X	F	32	Moderately advanced	L	Upper third	120	Honeycomb			Regressive	Stable	2
XI	M	32	Far advanced	R	Middle third	2	Single cavity	3 x 5	Thin	Regressive	Stable	1
XII	M	33	Far advanced	R	Upper third	8	Single cavity	5 x 5	Thin	Stationary	Stable	2
XIII	M	38	Far advanced and empyema	L	Upper third	84	Single cavity	7 x 7	Thin	Regressive	Stable	1

Si está afectado el otro pulmón, la enfermedad debe estar inactiva o estable en dicho lado.

Comprendido, pues, que el sexo y el lado afectado no revisten mayor importancia, parece desprenderse de este estudio que el enfermo ideal para una operación en el frénico sería una persona en el tercero o cuarto decenio de la vida, con una afección mínima de menos de un año de duración, localizada bien en los tercios superiores o medios del pulmón, y de preferencia en la fase regresiva. Los roentgenogramas deben revelar únicamente infiltración, o a lo más una sola caverna de paredes delgadas. El otro lado debe estar estabilizado.

INHALATION OF NEBULIZED PROMIN IN EXPERIMENTAL TUBERCULOSIS[1]

Sodium P,P′-Diaminodiphenylsulfone-N,N′-Didextrose Sulfonate

ALVAN L. BARACH, NORMAN MOLOMUT AND MAX SOROKA

Feldman, Hinshaw and Moses (1, 2) reported that P,P′-diaminodiphenylsulfone-N,N′-didextrose sulfonate had an inhibitory effect on the development of experimental tuberculous infection in guinea pigs. The compound was designated by the manufacturer as "promin."[2] They showed that the survival time of guinea pigs injected with a virulent human strain was increased and that the character and degree of the lesions indicate a definite inhibition of the disease (3). In these studies the average blood concentration of promin in 57 specimens was 4.3 mg., the lowest being 2.5 mg. and the highest 8.6 mg. per 100 cc. of blood. We repeated their experiments with slight variations in the procedure and then compared the effectiveness of the oral route with that of local application of the nebulized spray of promin. The latter method offered the possibility of greater concentration of the drug in the lungs with a lower blood concentration.

METHOD

Experiment I. Promin administered orally: Forty-three tuberculin-negative guinea pigs, weighing approximately 300 g. each, were separated into three groups as follows: (*a*) 15 untreated controls, (*b*) 13 treated with 400 mg. of promin orally and (*c*) 15 treated with 400 mg. of promin and 500 mg. of choline hydrochloride daily. The fact that administration of choline hydrochloride had caused regression in arteriosclerotic placques in rabbits previously fed cholesterol suggested its use as an adjuvant to promin, in the hope that this drug might affect the capsule of the tubercle bacillus. All of these animals were injected with 1 cc. of a freshly prepared suspension of tubercle bacilli, strain H.T. 37 R.V., grown on Petragnani's medium for fifteen days. The infecting dose contained a calculated dry weight of 0.5 mg. of organisms and was injected subcutaneously in the groin region. In all groups the therapy was started on the day of injection. Each animal was placed in a separate cage and the drugs administered by mixing with the food. The diet consisted of oats and hay supplemented by carrots and lettuce on alternate days. The oats were placed in special dishes and solutions of the drug poured over them. The food dishes were checked daily for completeness of consumption and the total amount given adjusted to that consumed. In order to insure ingestion of oats and drug, food was withheld during the day and given in the late afternoon. In practically all cases the food and drug were completely ingested. The experiment was continued for one hundred six days at which time all 15 of the untreated controls and all 13 of the promin fed animals had died. Four animals treated with promin and choline hydrochloride who were still alive were killed and necropsies done. Throughout the experiment all the animals were

[1] From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York, New York.

[2] The promin was supplied to us through the courtesy of Parke, Davis & Company, Detroit, Michigan.

autopsied at death or within fifteen hours (if death occurred during the night). Records of gross findings were taken. The tissues were fixed in Zenker's solution and prepared for histological examination for future examination.

Experiment II. Miscellaneous controls: As an additional check upon the specific effectiveness of promin for tuberculous infection in guinea pigs, a miscellaneous group of controls were treated as follows, and the results compared with those above: (*a*) 17 additional untreated controls; (*b*) 10 fed sodium salicylate orally, 0.5 g. daily; (*c*) 10 injected subcutaneously with Lederle's catarrhal vaccine, 0.2 cc. twice weekly; (*d*) 15 fed with 2.5 g. of egg yolk daily; and (*e*) 22 fed with 0.5 g. of choline hydrochloride daily. The total number of untreated and miscellaneous controls in this experiment was 74 guinea pigs.

In the administration of these drugs the procedure used was the same as in experiment I above, that is, mixing with the food. The infecting dose of organisms was 1 cc. of saline suspension of H.T. 37 R.V. injected subcutaneously in the groin and containing 0.5 mg. of organisms.

Experiment III. First group treated with promin administered by inhalation: Thirty-seven guinea pigs were separated into three groups as follows: (*a*) 10 untreated controls, (*b*) 4 normal animals treated with promin daily by inhalation and (*c*) 22 infected animals treated with promin by inhalation. The animals were injected subcutaneously with a 1 cc. suspension of H37 containing 0.5 mg. of organisms.

The apparatus used for the administration of the drug by inhalation consisted of a glass nebulizer,[3] which sprayed the promin solution in a fine suspension into a closed chamber. The volume of drug vaporized was calculated on the basis of 200 mg. of promin per pig per treatment. Each animal was placed in the closed chamber and inhaled the nebulized drug for a period of twenty-five minutes. This procedure was followed twice daily for forty-nine days at the end of which time all animals were sacrificed and pathological involvement compared on autopsy. Samples of tissue were fixed in Zenker's solution for further histological study.

Experiment IV. Second group treated by promin administered by inhalation: In experiment III above, the animals were injected with a culture of H37. This culture was a laboratory strain of low virulence and was not the same as used for experiments I and II above. Experiment III was reported with modification, using the virulent strain H.T. 37 R.V.

Forty-seven guinea pigs were divided into three groups and injected with 1 cc. suspension of H.T. 37 R.V. subcutaneously in the groin, containing 0.5 mg. of organisms: (*a*) 17 untreated controls, (*b*) 16 treated with promin by inhalation, 400 mg. per pig per treatment for forty-five minutes twice daily, and (*c*) 14 treated with 400 mg. promin orally per pig daily.

The procedures followed in administering the drug orally and by inhalation were described in experiments I and III above.

Blood promin determinations were made periodically during the course of this experiment. On the eighty-fourth day after infection all surviving animals were sacrificed and necropsies done. Specimens of tissues were fixed in Zenker's solution for further histological study.

[3] Supplied by the Vaponefrin Company, Upper Darby, Pennsylvania.

RESULTS

The appraisal of the results of these experiments were made on two bases, survival time and a comparison of the gross pathology at autopsy. The histological preparations were not relied upon for comparison because of the uneven sampling of tissue, but they will be studied later for the character of the lesions. Our autopsy protocols evaluating the gross pathological findings of lung, liver, spleen and lymph nodes were graded as follows:

– (negative): No gross evidence of tuberculosis.
1+: One to several minute epithelioid or fibrotic foci in the lung, liver and spleen, the latter being a normal size or slightly enlarged; no necrosis or caseation, lymph nodes slightly enlarged with or without fibrosis but without caseation or necrosis.
2: A moderate seeding of miliary tubercles or several large foci, single or conglomerate; lymph nodes moderately enlarged with beginning caseation, and with no or slight fibrosis.

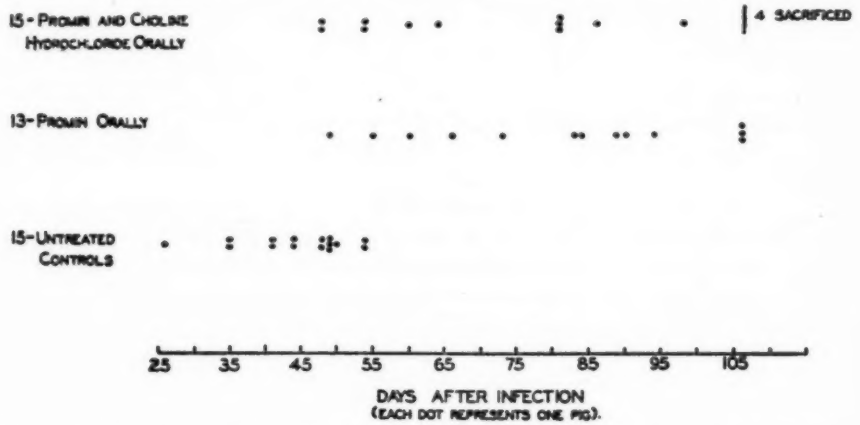


Chart 1. Distribution of death rate on days after infection with strain H.T. 37 R.V., 0.5 mg.

3+: Many large and conglomerate tubercles with beginning caseation or extensive miliary involvement; lymph nodes enlarged with caseation and with little or no fibrosis.
4+: Extensive progressive tuberculosis with large, conglomerate, necrotic, caseous areas; lymph nodes very large, completely caseous, necrotic and without fibrosis.

Experiment I. Promin administered orally: The autopsy results are summarized in table 1 and the distribution of survival is shown in chart 1. An examination of chart 1 will reveal that all the animals in the untreated control group were dead by the fifty-fourth day, while both groups receiving promin survived to the one hundred sixth day, with 4 animals in the group treated with promin and choline hydrochloride being alive on the one hundred sixth day when they were killed for necropsy. The distribution of survival of these two drug-treated groups was so nearly similar as to indicate no special value of addition of choline hydrochloride.

The comparison of the three groups on the basis of autopsy findings (table 1)

reveals that the promin treated group had the least generalized tuberculosis. The use of choline hydrochloride with promin did not enhance the therapeutic effect of promin. With respect to gross pathology, the promin plus choline fed group fared less well than the group treated with promin alone.

Experiment II. Miscellaneous controls: A comparison of the survival time of the guinea pigs treated with the various drugs indicated is present in chart 2. The distribution of deaths in all groups seems to be approximately the same as

TABLE 1

Gross pathological findings in guinea pigs infected with tubercle bacillus H.T. 37 R.V. and treated with promin orally

GROUP	NUMBER OF GUINEA PIGS	TREATMENT	DEGREE OF INVOLVEMENT ON AUTOPSY			
			1+	2+	3+	4+
A	15	Infected untreated controls	1	2	5	7
B	15	Promin orally daily	4	8	3	0
C	13	Promin and choline hydrochloride orally daily	2	4	4	5

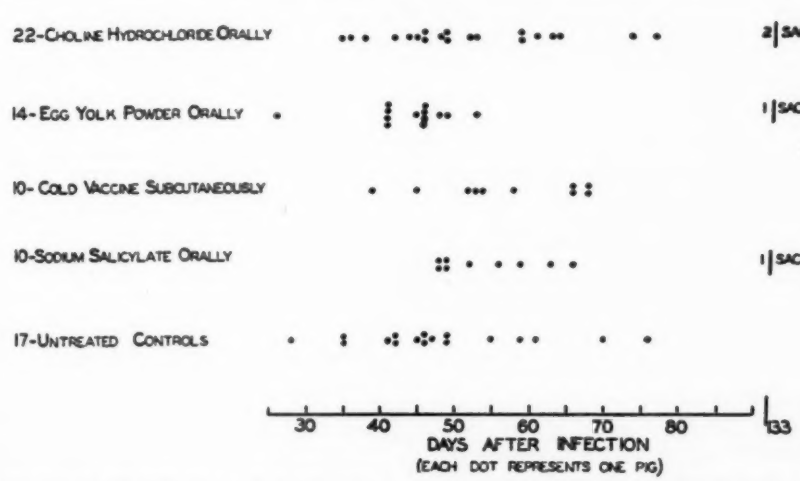


CHART 2. Distribution of death rate in untreated controls and miscellaneous controls after infection with strain H.T. 37 R.V., 0.5 mg.

for the untreated controls. The major number of deaths occurred between the fortieth and the seventieth day. This would indicate that these drugs had no effect on the development of tuberculous infection in guinea pigs.

A comparison of the gross pathological involvement of these animals also shows that there is little difference between the groups treated with the various drugs as compared with the untreated controls. The longer the survival time, the greater the pathological involvement. This was not true, however, in the animals treated with promin in experiment I. Despite the fact that the animals lived for twice the length of time as the controls, there was much less involvement.

Experiment III. First group treated with promin by inhalation: In this experiment, as noted above, the infecting organism was a markedly less virulent strain and the pathological involvement in all of the animals was considerably less than in experiments I, II and IV.

Group A: Uninfected, promin-treated control animals (4 guinea pigs). In all 4 of these animals the lungs exhibited several haemorrhagic areas with some fibrosis; these appear to be old haemorrhagic infarcts of varying ages. The remainder of the lung tissue and all other organs appeared normal.

Group B: Ten infected, untreated control animals. In all but one of these animals the lungs were found to contain several haemorrhagic areas and a moderate seeding of miliary tubercles. In the one exception the lungs were haemorrhagic but no tubercles were seen. The other organs showed an early form of generalized tuberculosis.

Group C: Twenty-two promin-treated, infected animals. In 50 per cent of the animals the lungs did not exhibit any tubercles on gross examination, merely a moderate amount of congestion with several haemorrhagic areas. The lungs

TABLE 2

Gross pathological findings in guinea pigs infected with tubercle bacillus H.T. 37 R.V. and treated with promin orally and by inhalation

GROUP	NUMBER OF GUINEA PIGS	TREATMENT	DEGREE OF INVOLVEMENT ON AUTOPSY				
			0	1+	2+	3+	4+
A	17	Infected untreated controls	0	0	0	9	8
B	16	Promin by inhalation	1	7	5	2	0
C	14	Promin orally	0	6	5	3	0

of the remaining 50 per cent of the animals exhibited a slight to moderate seeding of fibrotic tubercles and again many haemorrhagic areas. The other organs of these animals showed:

Liver: Tubercles present in only 2 animals.
Spleen: Tubercles present in only 3 animals.
Lymph nodes: Slightly enlarged in 50 per cent of the animals; 2 showed caseation and all else appeared normal.

These results suggested some definite therapeutic effect when promin was administered by inhalation, although the infection was not severe. The therapeutic effect was evident in the lungs as well as in the liver, spleen and lymph nodes. Since all the animals of three groups showed about the same number and intensity of haemorrhagic areas in the lung, promin did not appear to be injurious to the lung tissue. However, this experiment was terminated on the forty-ninth day in order to use the more virulent organism employed in experiments I and II above, with comparison of the results of the oral and pulmonary route of administration.

Experiment IV. Second group treated by promin administered by inhalation: The results of this study are presented again on the basis of survival time and gross pathology. The survival time distribution of the three groups is compared in chart 3. Thirteen of 16 animals treated with promin by inhalation survived for the duration of the experiment, eighty-four days. The deaths occurred on the twenty-third, fiftieth and fifty-ninth days. The animal that died on the twenty-third day showed evidence of a gallbladder obstruction which apparently contributed to his early death. The untreated controls, as well as the animals treated with promin orally, did not survive beyond the seventy-fifth day. Eight of the 14 animals treated with promin orally exhibited emphysema on autopsy not dissimilar from that observed in guinea pigs dead of anaphylactic shock. This was not observed in experiment I and may account for the difference in survival time between the orally fed animals of this experiment and those orally fed with promin in experiment I.

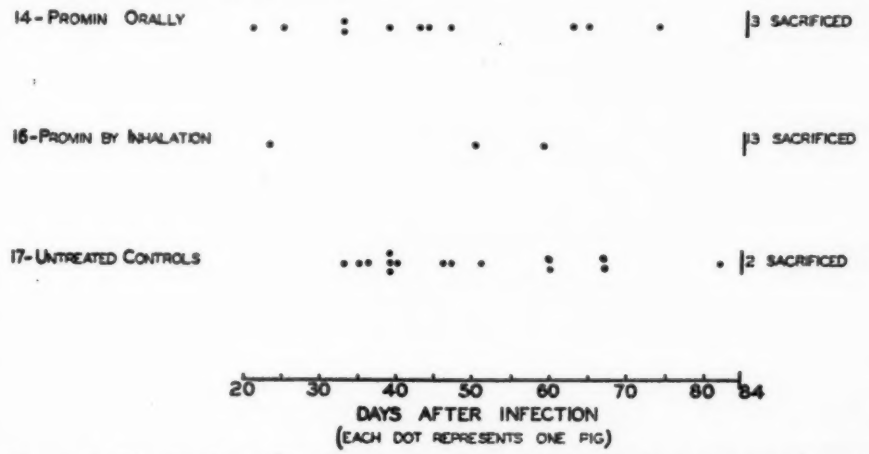


CHART 3. Distribution of death rate on days after infection in an untreated control group, a series treated with promin by ingestion and a series treated with promin by inhalation.

An analysis of the inhibiting effect of promin upon the extent of tuberculosis shows that all the anmals teated either by inhalation or oral administration had considerably less gross involvement than the untreated controls. One of the animals treated by inhalation of promin spray showed no gross evidence of tuberculosis. The average of both groups shows less generalized tuberculous infection in the guinea pigs treated by spray than in those treated by the oral route. With respect to the local involvement in the lungs, again the animals treated with promin by inhalation showed a slight but definite superiority over the promin-fed group as well as the untreated controls. The average lung involvement these groups is as follows:

Group A: Untreated controls 3.2+
Group B: Promin fed 2.5+
Group C: Promin by inhalation 1.5+ (with 2 animals showing no gross lesions of the lungs)

It is noteworthy that the average promin blood levels in the guinea pigs treated by inhalation was far less than the blood levels in those fed with promin. The results of 4 separate determinations are as follows:

Group B: Promin administered by mouth. Of a total of 20 blood levels determined on four separate occasions throughout the experiment, 2 tests showed no promin, 3 showed a trace and the remaining 15 had an average of 6.3 mg. per cent, the highest being 12 mg. per cent and the lowest 1 mg. per cent.

Group C: Promin by inhalation. Of 41 blood levels determined on four separate occasions throughout the experiment, 4 showed no drug, 17 showed a trace of the drug (below 1 mg. per cent) and the remaining 20 determinations showed an average of 1.68 mg. per cent, the highest determination being 5 mg. per cent, and the lowest 1 mg. per cent.

DISCUSSION

It is clear that administration of promin exercises a definite inhibitory influence on the development of experimental tuberculosis in guinea pigs. In the animal experiments of Feldman, Hinshaw and Moses, the drug was given by mouth. In the experiments which have just been reviewed inhalation of the nebulized spray of promin appeared to possess a superior value to the administration of the drug by mouth, even though the blood promin concentration was strikingly less in the group treated by inhalation. Not only was there less tuberculosis in the lungs of the guinea pigs who had inhaled the promin spray, but there was less generalized tuberculosis and a far higher survival rate. It seems likely that the ingestion of promin in the doses fed to the animals may have had unfavorable effects and thus contributed to the relatively higher mortality, although toxic manifestations in guinea pigs were not present in the series treated by Feldman, Hinshaw and Moses.

Our purpose in determining whether the inhalation route of administration would be effective in controlling experimental guinea pig tuberculosis was its ultimate application to man. In order to avoid the side effects of ingestion of the drug and the inconvenience of parenteral administration, the method of inhaling the nebulized spray of promin was first tried in animals. Inhalation of promin has since been used in 3 patients with advanced pulmonary tuberculosis, the results of which will appear in a subsequent publication. It must be borne in mind that some of the spray may be swallowed both in the animals as well as in human beings. The minimal concentration of the durg in the blood when given by inhalation indicates that at most only a small amount of promin found its way into the gastrointestinal tract. Since it has been shown that nebulized solutions penetrate to the depths of the lungs (4) it seemed possible that a high local concentration of the drug might be obtained in the absence of a high blood level. The practicability of vaporizing large amounts of neo-synephrin and epinephrine solutions with a continuous flow of oxygen from a high pressure tank has already been demonstrated (5).

These studies are intended to demonstrate the effectiveness of the inhalation

of the nebulized spray of promin in experimental guinea pig tuberculosis and not to prove that this method is necessarily superior to the oral route.

SUMMARY

A definite inhibition of the development of generalized tuberculosis was demonstrated in 28 guinea pigs infected with tubercle bacilli and treated by ingestion of promin, as compared to the gross autopsy result observed in 88 untreated and miscellaneous control animals.

The inhalation of the nebulized spray of promin had a deterrent influence on the development of generalized tuberculosis in 22 guinea pigs, as compared to 10 infected, untreated control animals.

Comparison was made of the degree of generalized gross tuberculosis in guinea pigs treated by ingestion of promin and by inhalation of the nebulized spray. Despite a far lower blood concentration of promin in animals who had inhaled the nebulized spray, the degree of pulmonary as well as generalized tuberculosis was less than in the orally fed group. Furthermore, of 16 animals treated by inhalation of the nebulized spray of promin, 13 survived for the duration of the experiment, namely eighty-four days, whereas all of the 14 animals given promin by mouth and the 17 untreated animals did not survive beyond the seventy-fifth day.

Inhalation of the nebulized spray of promin appears to have the advantage of a high local concentration of the drug in the lung with a minimal blood concentration. This method has been carried out in 3 patients with advanced pulmonary tuberculosis and will be reported in a later communication.

SUMARIO

En 28 cobayos infectados con bacilos tuberculosos y tratados con promina por vía bucal, observóse una inhibición bien definida del desarrollo de la tuberculosis generalizada, comparada con los resultados autópsicos macroscópicos en 88 animales testigos no tratados y varios.

La inhalación de nébulas de promina ejerció un influjo adverso al desarrollo de tuberculosis generalizada en 22 cobayos, comparados con 10 animales testigos no tratados infectados.

Compárase la intensidad de la tuberculosis macroscópica generalizada en los cobayos tratados con promina por vía bucal y con inhalaciones de nébulas. A pesar de una concentración sanguínea mucho más baja de promina en los animales que inhalaron, la intensidad de la tuberculosis pulmonar y generalizada fué menor en ellos que en el grupo tratado por vía bucal. Además, de 16 animales tratados por inhalación, 13 sobrevivieron toda la duración del experimento, a saber, ochenta y cuatro días, mientras que ninguno de los 14 animales que recibieron promina por vía bucal, o de los 17 no tratados, sobrevivió más allá del septuagésimoquinto día.

La inhalación de nébulas de promina parece poseer la ventaja de que obtiene una elevada concentración local de la droga en el pulmón, con una concentración

sanguínea mínima. Esta técnica ha sido aplicada en 3 enfermos con tuberculosis pulmonar avanzada, y será descrita en una comunicación subsecuente.

BIBLIOGRAPHY

(1) Feldman, W. H., Hinshaw, H. C., and Moses, H. E.: The effect of promin (P,P'-Diaminodyphenylsulfone-N,N'-Didextrose Sulfonate) on experimental tuberculosis, A preliminary report, Proc. Staff Meet. Mayo Clin., 1940, *15*, 695.

(2) Feldman, W. H., Hinshaw, H. C., and Moses, H. E.: The treatment of experimental tuberculosis with promin (P,P'-Diaminodyphenylsulfone-N,N'-Didextrose Sulfonate), A preliminary report, Ibid., 1941, *16*, 187.

(3) Feldman, W. H., Hinshaw, H. C., and Moses, H. E.: Promin in experimental tuberculosis, Am. Rev. Tuberc., 1942, *45*, 303.

(4) Castex, M. R., Capdehourat, E. L., and Pedace, E. A.: Inhalacion de Substancias Nebulizadas: Comprobacion Experimental de su Poder de Penetracion a Nivel del Aparato Respiratorio, Arch. argent. de enferm. d. ap. respir. y tuberc., March-April, 1941, *9*, 1.

(5) a-Richards, D. W., Jr., Barach, A. L., and Cromwell, H. A.: Use of vaporized broncho-dilator solutions in asthma and emphysema, Am. J. M. Sc., 1940, *199*, 225.

b-Barach, A. L.: Physiological methods in the diagnosis and treatment of asthma and emphysema, Ann. Int. Med., 1938, *12*, 454.

CHEMOTHERAPY OF TUBERCULOSIS[1]

Promin[2] by the Intravenous Drip Method

GARY ZUCKER, MAX PINNER AND HAROLD THOMAS HYMAN

The purpose of this paper is to present the findings in a group of 12 tuberculous patients treated with promin administered by the continuous intravenous drip method. The rationale of this form of administration has been discussed in previous publications (1, 2). Promin was selected for study following the favorable report of its inhibitory action against tuberculosis of the guinea pig, by Feldman, Hinshaw and Moses (3). These investigators found that in two experiments (3, 4, 5) a large percentage of the infected animals receiving promin by mouth lived longer and had less extensive and more proliferative tuberculosis than the untreated controls. Approximately 50 per cent of the treated animals did not show any gross or microscopical evidence of tuberculosis. This latter group consisted of guinea pigs in whom promin had been started two days before infection, the day of infection and three days, one week, two weeks, four weeks and six weeks later.

METHOD

The continuous intravenous drip method was started in a forearm vein at 9 a.m. and allowed to run for ten hours.[3] This procedure was followed on each week-day. No therapy was given over the week-ends. This was done to prevent signs of chronic toxaemia and undue phlebitis. The initial dose of promin each morning consisted of 5 g. given as a 5 or 10 per cent solution in 5 per cent glucose in distilled water. This was run in over a period of eight to ten minutes. The drip was then continued at 20 to 30 drops per minute with a 1 per cent solution of promin in 5 per cent glucose in distilled water, if 15 g. were to be given daily, or with a 2 per cent solution of promin if 25 g. were to be given daily. The total fluid intake intravenously was, therefore, not more than 1,100 cc. daily. In most of the patients this procedure was followed for four consecutive weeks. Four patients received a second course of four weeks of therapy after a rest period of five days to three weeks.

DOSAGE

The daily dosage varied between 15 g. and 25 g.[3] This was equivalent to 300 to 340 mg. of promin per kilogram of body weight. Two patients (cases 6 and 12) received 450

[1] This investigation was carried out as part of the deJonge Tuberculosis Project on the Division of Pulmonary Diseases, Montefiore Hospital for Chronic Diseases, New York, New York.

[2] Promin (Sodium P,P′-Diaminodiphenylsulfone-N,N′-Didextrose Sulfonate) was supplied by Dr. E. A. Sharp, Parke, Davis & Company.

[3] In case 11, a thirteen month old infant, the continuous drip was often set up in a scalp vein and the saphenous vein as well as the antecubital veins. In this patient a continuous drip of 1 per cent promin in 5 per cent glucose in distilled water or in physiological saline was given for twenty-four hours daily and every day of the week; 6 g. of promin (600 mg. per kilo) were administered daily until the time of death, twelve days later. During the last eight days 2 g. of promin were also given by mouth. (Treatment of this patient was carried out on the private service of Dr. Camille Kereszturi at Babies Hospital, New York, New York.)

to 470 mg. per kilogram for one week but because of toxic symptoms the dosage was reduced to the more tolerable levels of 300 to 340 mg. per kilogram. The total amount of drug received by each patient varied with the size of the patient and the duration of treatment.

PHARMACOLOGY

Promin is the sodium salt of P,P′-diaminodiphenylsulfone-N,N′-didextrose sulfonate. About 50 per cent of its molecule is made up by glucose. It is freely soluble in water and is prepared as a 40 per cent solution for intravenous use. As noted above, much more dilute solutions were used in our work in order to make administration by the continuous drip possible. Blood levels of free promin were determined before the drip was started in the morning and after fifteen to thirty minutes and four, eight and twenty-four hours (table 1). On the whole these levels were much higher than when promin was given intravenously in doses of 5 g. each at two and one-half hour intervals. With the latter method, promin levels of 5.8 to 21.6 mg. per cent were found fifteen to thirty minutes after injection. After two hours these had fallen to 2.8 to 4.0

TABLE 1

Range of free promin blood levels in 5 patients during one day of treatment. Determinations were made before and at intervals after the start of the continuous intravenous drip of promin. The drip was discontinued after ten hours

BEFORE	15–30 MINUTES	4 HOURS	8 HOURS	24 HOURS
mg per cent	*mg per cent*	*mg per cent*	*mg per cent*	*mg per cent*
1.3–3.0	8.9–12.6	5.0–13.1	6.9–15.4	1.7–2.7

mg. per cent. The blood levels obtained with the parenteral administration of promin are relatively low when one considers the large doses given in a ten-hour period. This can be attributed to the rapid rate of excretion and to the fact that glucose comprises about half of the molecular weight of promin.

TOXICOLOGY

The toxic effects of promin were for the most part slight and transient. These included fever occasionally up to 101°F. and slight anorexia, cyanosis, weakness, headache and drop of haemoglobin (0.7 g. to 1.4 g.). One patient (case 7) developed an acute haemolytic anaemia with a decrease of haemoglobin from 12.7 g. to 7.8 g. after receiving 200 g. of promin in two weeks. The haemolytic process stopped when promin was discontinued. Local venous thickening and thromboses were observed in several patients but did not interfere with continuation of therapy. A transient and mild albuminuria was noted in one case. In 2 patients (cases 6 and 12), receiving 25 g. of promin daily (450 to 470 mg. per kilo), blood levels were maintained between 10 and 15.4 mg. per cent. In these patients the common toxic symptoms of sulfanilamide were noted. These included fever, rash, pruritus, headache, dizziness, anorexia, nausea and marked

cyanosis. These symptoms disappeared promptly when the daily dose was cut to 15 g. (300 to 340 mg. per kilo). It has been our impression that the apparent nontoxicity of promin administered intravenously is due, in part, to the relatively low concentration that is usually obtained in the blood. When higher concentrations are maintained toxic symptoms are obvious.

LENGTH OF OBSERVATION

The patients were observed for from four to seven months after treatment with promin was started. Three patients (cases 10, 7, 11) died eight, five and two weeks, respectively, after receiving promin. The evaluation of the status of each surviving patient was made after an interval of three months. In no case was there any reason to alter this judgment after four to seven months of observation. The reasons for the short period of treatment and observation are presented below in the discussion.

CLINICAL MATERIAL AND RESULTS

Twelve patients were treated. All patients had been on bed-rest from one month to two years prior to promin therapy. One patient (case 9) was also receiving pneumothorax refills. Of the 12 patients, objective evidence indicated that on bed-rest there had been progression in 8, no change in one and slight improvement in 3. The bed-rest regimen was continued in each case while promin was administered.

The classification and the salient features of each case are as follows:

Minimal Tuberculosis..... 1

Case 1: (W. F.) A fifty-four year old white male. Reactivation of an old focus in the apex of the right lower lobe began three months prior to promin therapy. Slight progression, but no cavitation, had occurred during this period. This patient had an active, granulomatous and stenosing tuberculous laryngitis for which a tracheotomy had been performed in 1940. The laryngeal lesion had been slowly progressive with temporary periods of remission in spite of voice-rest, cautery and deep X-ray treatment. Five hundred and forty g. of promin were given intravenously over a seven and one-half week period; 29 g. of promin were also administered by inhalation of a 20 per cent solution of promin from a vaporizer.[4] The pulmonary lesion slowly increased in size and excavated during the course of chemotherapy. The laryngeal lesion remained essentially unchanged.

Moderately Advanced..... 4

Case 2: (S. S.) A twenty-nine year old white male. Pulmonary and constitutional symptoms appeared four months before chemotherapy. X-ray films of the chest showed a mainly exudative lesion of the right upper lobe without evidence of cavitation. Slight improvement had occurred on bed-rest. One thousand g. of promin were given over an eight-week period. Slight resorption of the lesion was observed and the sputum and gastric contents became negative shortly after promin was started. However, five months later, while on bed-rest, the sputum was again found to be positive.

[4] The daily dosage was gradually increased from 0.4 g. to 0.8 g. given in four equal doses. This method of local application was used in an effort to augment the possible effect of promin on the laryngeal lesion.

Case 3: (G. G.) A thirty-two year old Negro male. Pulmonary and constitutional symptoms began three months prior to chemotherapy. X-ray examination of the chest revealed a mainly exudative tuberculosis of the hilar region of the left lower lobe without evidence of cavitation. Slight increase in size of the lesion had occurred on bed-rest. One thousand g. of promin were administered intravenously over an eight-week period. During this time the general condition of the patient improved but the pulmonary infiltration progressed and excavated.

Case 4: (S. M.) A twenty-nine year old white male. Pulmonary and constitutional symptoms occurred five months before promin therapy was instituted. Radiographically, there was a mottled infiltration of the right upper lobe without definite evidence of cavitation. Slight clinical and radiographic improvement had occurred on bed-rest. One thousand g. of promin were given over an eight-week period. Very slight resorption was seen on the X-ray films and the sputum remained positive. The general condition of the patient was moderately improved.

Case 5: (S. T.) A fifty-one year old white male. Pulmonary and constitutional symptoms appeared six months before chemotherapy. At that time serial X-ray films of the chest disclosed a new lesion involving the apex of the right upper lobe. This contained a cavity 2 cm. in diameter. On bed-rest, no change was observed in this lesion. One hundred and eighty-six g. of promin were given intravenously over a period of eleven days. Treatment was interrupted at the request of the patient. Serial X-ray films and follow-up examination revealed no change.

Far Advanced 4

Case 6: (T. J.) A twenty-nine year old white female. X-ray films of the chest showed old fibrocavitary, probably haematogenous, tuberculosis of both upper lobes. Repeated local exacerbations with slow progression had occurred on bed-rest. Three hundred and forty-five g. of promin were administered over a four-week period. No changes were noted following chemotherapy.

Case 7: (M. K.) A thirty-four year old white male. This patient had an extensive caseocavernous tuberculosis of the left lung which had not been controlled by artificial pneumothorax. The latter had been abandoned. One month prior to chemotherapy a spread was noted in the right lower lobe. Slow progression was observed on bed-rest. Two hundred g. of promin were given over a two-week period. Treatment was stopped because of marked general toxaemia and the appearance of an acute haemolytic anaemia. The disease continued to progress and the patient died three weeks later.

Case 8: (K. F.) A thirty-nine year old white male. This patient had an old fibrocavitary lesion of the left upper lobe for which he was being treated with bed-rest. Serial X-ray films revealed the development of an exudative lesion about one inch in diameter in the right upper lobe only two and one-half weeks prior to chemotherapy. Two hundred and ninety-six g. of promin were given over a four-week period. The fresh lesion in the right lung progressed and excavated during promin therapy. In addition, symptoms and radiographic signs of ileocaecal tuberculosis appeared.

Case 9[5]: (H. C.) A twenty-one year old white female. Radiographic onset of minimal tuberculosis four months prior to promin therapy. This lesion progressed and excavated while the patient was on bed-rest. Left pneumothorax was induced but a fresh spread developed in the right lower lobe one month before chemotherapy was started. Three hundred g. of promin were given over a four-week period but the lesion continued to progress.

Miliary Tuberculosis 1

Case 10: (H. M.) A twenty-seven year old white male. This patient had a left nephrectomy for tuberculosis of the kidney. Miliary tuberculosis developed eight weeks later. After seven weeks of bed-rest, slight clinical improvement had occurred. Two hundred and eighty-three g. of promin were then administered over a four-week period. At the conclusion of this interval the pulmonary lesions had progressed and a fatal tuberculous meningitis set in.

Tuberculous Meningitis 1

Case 11: (B. P.) A one year old white, male infant. Primary infection tuberculosis of the right lung was diagnosed radiographically six months before chemotherapy. Meningeal symptoms and signs were present for six days when promin was instituted. Eighty-five g. of promin were given intravenously and 19.5 g. orally over a twelve-day period. At this time the patient died of a tuberculous meningitis.

Tuberculous Tracheitis and Bronchitis 1

Case 12: (L. P.) A thirty-nine year old white female. This patient had an old, unsuccessful six-rib thoracoplasty on the right side. There was extensive ulcerocaseous tuberculosis of the right main bronchus and the lower part of the trachea of two years' duration. Gradual progression of the ulceration accompanied by slight stricture of the trachea had occurred on bed-rest and in spite of cauterization with silver nitrate. Three hundred and forty-five g. of promin were given over a four-week period. Following chemotherapy the patient developed several episodes of stridor with sputum retention. Repeated bronchoscopic examinations revealed progressive stenosis of the trachea. Simultaneously the ulcerations became less extensive and more fibrotic. The bronchoscopists were of the opinion that the rate of healing was faster than could be anticipated.

The final results can be summarized as follows:

Improvement	3	(Cases 2, 4 and 12)
No change	2	(Cases 5 and 6)
Progression	4	(Cases 1, 3, 8 and 9)
Died	3	(Cases 7, 10 and 11)

DISCUSSION

The effect of chemotherapy can best be judged in patients with relatively early and nondestructive tuberculosis. Therefore, an effort was made to select

[5] We are indebted to Dr. David Carr, Chief Resident on the Chest Service of Dr. J. Burns Amberson at Bellevue Hospital for his coöperation in carrying out the treatment of this patient.

patients with that type of lesion, to treat them for one to two months and to compare these results with what could be expected on a similar period of bed-rest. Cases 1, 2, 3, 4 and 5 had limited lesions of short duration and in only one was any cavitation demonstrable. Cases 6, 7, 8 and 9 had far advanced tuberculosis, but each had distinct fresh infiltrations of two and one-half weeks' to three months' duration. In these patients the effect of treatment was evaluated on the basis of the course of the new lesions. Case 10 had a miliary tuberculosis of seven weeks' duration. The discrete, haematogenous tubercles most closely resemble the lesions of experimental tuberculosis in guinae pigs and should theoretically be most amenable to chemotherapy. Case 11 also had an early lesion but one that is usually fatal. Case 12 was selected essentially to note the effect of promin on a chronic ulcerocaseous tuberculosis of the trachea and bronchus. Not only did the location of the lesion make direct visualization of any changes possible, but also previous observations on the treatment of mucosal tuberculosis with sulfanilamide suggested that such lesions might respond differently than pulmonary ones (2).

Promin did not alter the expected course of the disease in any of the patients, with the possible exception of one (case 12). The improvement noted in 2 patients (cases 2 and 4) was not any better than is often found for such lesions on bed-rest alone. The rate of clearing and fibrosis of the ulcers of the trachea and bronchus in case 12 was unexpected and may signify some therapeutic effect. This observation requires further study. The progression occurring in 4 patients is particularly significant, since in all of them the lesions were early and nondestructive. In case 8 not only did the new pulmonary infiltrations progress and excavate during and after treatment, but symptoms and radiographic signs of intestinal tuberculosis appeared.

Although this series is small, we believe that the criteria used in the administration and evaluation of treatment make it possible to reach a valid conclusion. We have applied the following principles in carrying out our investigations of the experimental treatment of clinical tuberculosis.

(*1*) The most suitable cases for chemotherapeutic attempts are those with early and predominantly exudative tuberculosis without evidence of massive tissue destruction or considerable fibrosis. Little is to be expected from the treatment of old fibroid and cavitary tuberculosis. The experience obtained from the more recent advances in chemotherapy of bacterial and spirochaetal diseases indicates that the best results are obtained in the earliest stages of infection when resolution of the inflammatory process is possible and when the obstacles of fibrosis and tissue destruction are not as yet present.

(*2*) The drug should be given up to the limit of the patient's tolerance. This procedure will assure the maintenance of high concentrations of the drug in the tissues without undue toxic effects. In addition, if high blood levels are a factor in the therapeutic action of the drug then the fullest effect will be obtained in a single experiment.

(*3*) The results obtained with effective chemotherapy should be consistently better than the best that can be expected from bed-rest alone. In the type of

patient described above, significant resorption of a recent, nondestructive lesion may occur on bed-rest as early as two to three months. This improvement may be associated with sputum conversion and subsidence of laboratory and clinical evidences of activity of the disease process. Roentgenological disappearance of the lesion and of the signs of tuberculous activity may be complete in from four to eighteen months or more, depending on the age, type and extent of the disease and the constitutional make-up of the patient. Therefore, when testing for the possible therapeutic action of a new drug, a demonstrable beneficial effect should manifest itself soon after treatment is started and it should be definite within two to three months. If no unusual improvement is noted after one to two months of intensive treatment, then it is probable that the drug is not effective against clinical tuberculosis. If a longer period of treatment or observation is used, any improvement might be attributable to bed-rest and not to the drug. It should be clearly understood that these principles apply only to work for the *evaluation of new drugs*. Once evidence is on hand that a drug has some definite beneficial action, prolonged treatment is probably indicated. But in the experimental stage, no elucidation may be expected by treatment over many months or by observation periods of many months following the treatment, because an indefinite number of variables, immanent in the natural course of the disease, will entirely becloud the issue. For such prolonged observations, a few patients are usually found—out of a large number of initial patients—who show remarkable improvement which is then frequently ascribed to the particular treatment, although a small percentage of patients will show unexpected improvement on bed-rest and even without any treatment at all. Control cases do not help to segregate such exceptional developments, unless hundreds of cases be observed.

(*4*) Because of the extreme variability of human tuberculosis, only definite and fairly consistent evidence of improvement following chemotherapy should be taken to indicate efficacy of the drug.

(*5*) The criteria for judging therapeutic action should be objective radiographic, clinical and laboratory signs. Little value should be placed on the subjective reaction of the patient.

It is our contention that, if a new drug is employed according to the above principles and if unusual and unexpected improvement is not obtained, the drug as given is ineffective against clinical tuberculosis. This is the conclusion that we have reached with promin administered by the intravenous drip method. Our clinical observations are at variance with the successful results in tuberculous guinea pigs. The reason for this discrepancy is at present not known. It should serve to emphasize again the difficulty of translating laboratory experience in tuberculosis into the clinical experiment. Guinea pig tuberculosis differs from human tuberculosis not only in the virulence and dosage of the infecting organism and the mode of infection, but also in the pathogenesis of the infection, the resistance of the host, the type and distribution of the tuberculous lesions and the course and duration of the disease. Furthermore, the action of drugs may not be the same in the guinea pig and man. The latter point has been partic-

ularly well demonstrated for promin. Guinea pigs can tolerate large doses of promin by mouth but in man comparatively minute doses are very toxic when administered orally. However, one cannot minimize the importance or the significance of the ability of a sulfanilamide drug to retard experimental guinea pig tuberculosis. The clinical findings are disappointing at present, but they make it necessary more than ever to extend the search for a drug that will cure tuberculosis. This may be accomplished by extensive chemical research into new drug combinations and careful application of these drugs to the earliest stages of human tuberculosis.

SUMMARY

1. Large doses of promin were administered by the continuous intravenous drip method to 12 patients with pulmonary tuberculosis.

2. Toxic signs were few and slight. One patient developed an acute haemolytic anaemia of moderate severity.

3. No beneficial effect was observed in our patients. Unexpected healing of a tracheobronchial ulceration was noted in one case. This observation requires further study.

4. A set of criteria for the conduct of our experiment on the chemotherapy of clinical tuberculosis is presented.

SUMARIO

1. A 12 tuberculosos pulmonares se les administraron dosis masivas de promina mediante el sistema de goteo intravenoso corriente.

2. Los signos de toxicidad fueron escasos y leves. Un enfermo manifestó una anemia hemolítica aguda de mediana gravedad.

3. No se observó efecto beneficioso en los enfermos, pero en un caso se notó la cicatrización inesperada de una úlcera traqueobronquial, exigiendo esta observación estudio más detenido.

4. Preséntase la serie de reglas por que se rigió este experimento relativo a la quimioterapia de la tuberculosis pulmonar.

We wish to acknowledge our appreciation to Mr. Edward Weinbaum of the Medical Research Laboratories of Montefiore Hospital for performing the promin determinations.

BIBLIOGRAPHY

(1) HYMAN, H. T.: Massive dose chemotherapy by the intravenous drip method, Bull. New York Acad. Med., 1941, *17*, 135.

(2) ZUCKER, G., PINNER, M., AND HYMAN, H. T.: Chemotherapy of tuberculosis: Sulfanilamide by the Intravenous Drip Method, Am. Rev. Tuberc., 1942, *45*, 292.

(3) FELDMAN, W. H., HINSHAW, H. C., AND MOSES, H. E.: The effect of promin on experimental tuberculosis, Proc. Staff Meet. Mayo Clin., 1940, *15*, 695.

(4) FELDMAN, W. H., HINSHAW, H. C., AND MOSES, H. E.: Treatment of experimental tuberculosis with promin, Ibid., 1941, *16*, 187.

(5) FELDMAN, W. H., HINSHAW, H. C., AND MOSES, H. E.: The deterrant effect of promin on experimental tuberculosis, Am. Rev. Tuberc., 1942, *45*, 303.

B-COMPLEX DEFICIENCY IN TUBERCULOSIS

Gastrointestinal Manifestations

W. H. GLASS[1]

The nonspecificity of therapy that is used in the modern treatment of pulmonary tuberculosis necessarily brings into play all factors in modern medicine and surgery. The problem of nutrition in any chronic disease has always been a paramount issue. In tuberculosis, more specifically, pulmonary tuberculosis, the body response to the toxins of the invading organism entails almost invariably some degree of anorexia. Not infrequently the degree of anorexia is so intense that this is the presenting problem.

With the advent and development of the current concept of vitamins, rapid application has been made of the use of this knowledge in the therapy of tuberculosis. Unfortunately, to date, the methods of analysis of vitamin content of body fluids are too complicated for ordinary hospital use. Even in institutions where detailed chemical analyses and the help of biological chemists are available, not infrequently, the laboratory results do not jibe with the clinical findings. The factors of intake, absorption, utilization and excretion of the various components of the vitamins are still not sufficiently well understood so that the faulty factor, if it exists alone, could be isolated from the others and treated.

In the treatment of any large number of patients with pulmonary tuberculosis one is immediately struck with the variability and intensity of abdominal complaints. On rounds in a tuberculosis sanatorium the complaint of "stomach trouble" or "bowel trouble" is more frequently encountered than complaints referable to the known site of the disease process. Because the incidence of intestinal tuberculosis is so great pathologically, being reported in some studies as high as 92 per cent (1, 2), clinically one is prone to make this diagnosis too glibly. If the patient continues to retrogress, and comes to pathological study the high incidence of involvement would tend to verify the clinical diagnosis in many cases. In contrast to this 14 to 50 per cent (1) of intestinal tuberculosis is first diagnosed at the autopsy table, although extensive ulcerative involvement of the small and large bowel may be present.

Pathologically intestinal tuberculosis is found almost invariably at the ileocaecal junction. Because of the frequency of its localization at this point, roentgenographic investigation is aimed primarily at the visualization of these segments of the gut. The technique in common use is for the opaque meal to be ingested six to eight hours prior to fluoroscopic visualization, and then for films to be taken as deemed necessary by the examiner. Using this method, the stomach and upper intestinal tract are seen only incidental to the focused point in the right lower quadrant, and then only if sufficiently large films are used. At this time, six to eight hours after the barium is swallowed, only residua remain in the upper intestinal coils and any detailed mucosal studies cannot be adequately carried out.

[1] Cedarcrest, Hartford, Connecticut.

Inasmuch as the current diagnostic and therapeutic methods relating to intestinal tuberculosis are not ideal or even good, it was felt that any investigation leading towards further elucidation of this confusing picture warranted reporting. Following a fairly detailed study of 3 patients with pulmonary tuberculosis whose primary complaints were all abdominal and in whom retrogression and ultimate death appeared inevitable, it was felt that by the application of intensive B-complex therapy their courses have been sufficiently altered to warrant further application of this therapy.

During the past decade a definite description of a syndrome due to deficiency of the vitamin-B complex has been evolved. Mackie (3) in 1933 is credited with the first description of the functional changes in the small intestine which are now acknowledged to be due to a deficiency of vitamin-B complex. This and subsequent reports (4, 5, 6) during the subsequent few years dealt primarily with descriptions of sprue and sprue-like entities (nontropical sprue, idiopathic steatorrhoea, and coeliac disease). Further investigation (5, 6, 7, 8) has led to the assumption of the identity or very close relationship of these diseases. During the past year adequate summaries of the work done in various clinics were given by Mackie (9), Golden (10) and Lepore and Golden (11). A report of the experimentally produced gastrointestinal changes in animals is given by Heublein and his associates (12).

The clinical picture of the B defficiency syndrome in patients uncomplicated by tuberculosis is essentially one of asthenia. The complaints are those of weight loss, anorexia, mental irritability, generalized weakness, flatulence, abdominal pain, diarrhoea and/or constipation. Inasmuch as the symptoms of pulmonary tuberculosis or combined pulmonary and intestinal tuberculosis can very closely simulate these complaints, one or all of these manifestations could be attributed to the site of the known disease process. Lepore and Golden (11) list the objective findings as follows:

1: Flat oral dextrose tolerance curve
2: Abnormal small intestine roentgen-ray appearance
3: Malnutrition
4: Hypochlorhydria or achlorhydria
5: Increased capillary fragility
6: Absence of steatorrhoea, glossitis, dermatitis or anaemia of significant degree
7: Eighty per cent of the patients are women

The establishment of the diagnosis in this investigation was based primarily on the roentgenographic appearance. It is felt that the other factors, as listed above, would be influenced by the presence of advanced and active pulmonary tuberculosis. The following case reports are submitted in fair detail to show how, especially in case 2 and less so in case 3, the course of the pulmonary disease has been influenced by adequate vitamin-B therapy.

CASE REPORTS

Case 1: F. DeV. White female, age forty, married, two children, housewife.

This patient entered Cedarcrest on February 27, 1941 with a complaint of diarrhoea of eight months' duration. Her past history is essentially negative. Eight months

prior to admission she was hospitalized for "rectal fissure." This was operated upon and was followed by infection and diarrhoea, since which time she has been bed-ridden. Her menses, which previously had been regular and painless, ceased at about this time and have not recurred. She dates the onset of her present illness to the operative procedure on her rectum. Since then there has been persistent diarrhoea with defecation preceded by cramp-like pains and great urgency. Her maximum weight several years ago was 118 pounds. Her admission weight to this institution was 68 pounds. She relates that the major loss in weight has occurred since the onset of diarrhoea. At no time during her present illness has there been any cough or expectoration, but she has had frequent episodes of temperature elevation. The record of her previous periods of hospitalization shows repeated negative examinations for tubercle bacilli in the sputum, with tubercle bacilli found on one occasion in the gastric contents. Her urine was repeatedly negative for acid-fast bacilli. Discharge diagnoses were: (*1*) pulmonary tuberculosis; (*2*) ulcerative colitis (tuberculous); (*3*) tuberculosis of the gastrointestinal and genitourinary tracts; (*4*) Simmond's disease.

On admission she was markedly emaciated and pallid and appeared to be of the stated age. She gave the impression of being chronically and acutely ill. Her temperature varied between 97°F. and 101.6°F. There was marked emotional instability. Blood pressure was 85/0. Physical examination of the heart and lungs was negative except for roughened vesicular breath sounds. The abdomen was protuberant with tense skin covering symmetrical, markedly dilated superficial veins. There was a well-healed appendectomy scar. Pressure of the examining hand elicited a diffuse soreness with deep pain in the left lower quadrant. The abdomen felt doughy with perceptible rolling of gas under the examining hand. There was a tympanitic percussion note throughout. Her anus showed a right lateral muco-cutaneous incision which appeared to be granulating. There was a diffuse mucous membrane inflammation. Digital examination of the rectum was not possible because of the marked pain. Her admission laboratory findings are as follows: no sputum raised for examination; urine, specific gravity 1.012, trace of albumin, innumerable leucocytes, moderate number of epithelium cells, numerous calcium oxalate crystals and many bacteria; sedimentation rate (modified Westergren) one hour 46.5 per cent, two hours 65 per cent; haemoglobin 9 g. or 64.3 per cent, erythrocytes 3,040,000, leucocytes 5,150 with 78 per cent polymorphonuclears and 30 per cent nonlobulated forms, lymphocytes 17 per cent, mononuclears 1 per cent and eosinophils 4 per cent. The red cells showed marked poikilocytosis and anisocytosis, many cells showed polychromatophilia with basophilic stippling; one erythrocyte with mitotic nucleus was seen. Kline exclusion test was negative. Gastric contents were negative for tubercle bacilli. Gastric analysis with alcohol and histamine showed a moderate hyperacidity with the highest total acidity of 94 after histamine stimulation. On admission, flat film of the chest showed a calcified Ghon focus in the right lower lobe and well calcified, apparently inactive residua at the extreme right apex. The admission diagnosis was pulmonary tuberculosis, right, inactive; tuberculous enterocolitis.

The patient was placed on a nonresidue diet, given gastric sedation, iron by mouth in large quantities, and an only partially successful attempt was made to control her diarrhoea with tincture of opium and bismuth subcarbonate by mouth. Reëxamination of her peripheral blood one month after admission showed a slight increase in the haemoglobin to 11 g. with an almost identical white blood cell count and differential.

During the first six months of her current hospitalization she showed fairly steady retrogression. Faeces examinations on two occasions were positive for tubercle bacilli.

Her blood continued to show advanced anaemia. Anorexia and diarrhoea persisted and she developed a marked ankle, pretibial and sacral oedema on a hypoproteinaemic basis with a reversal of the albumin-globulin ratio. Because of her increasing amount of oedema she was given repeated dosages of intravenous mercurials and xanthines. The diureses produced were only incomplete and her oedema with beginning anasarca continued.

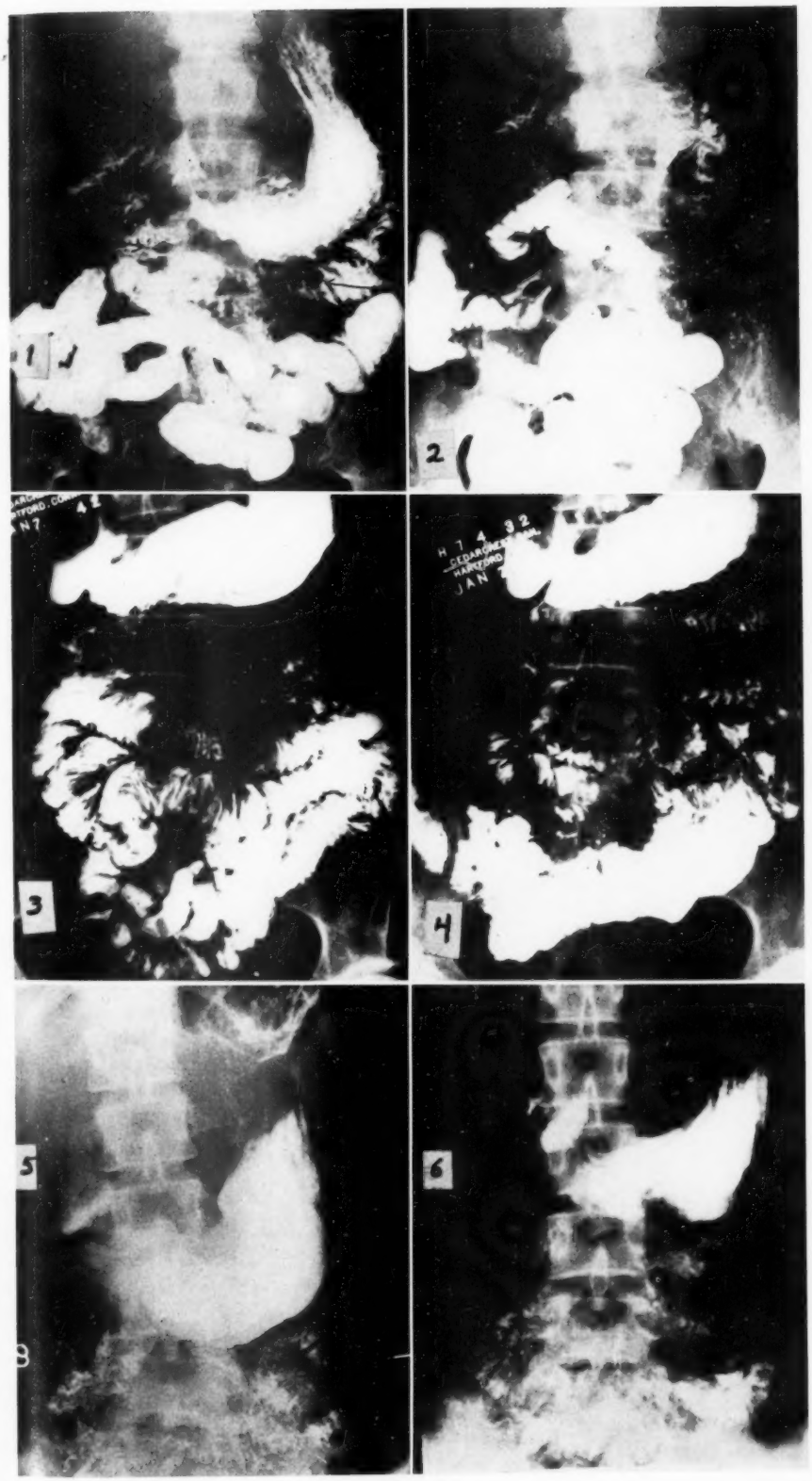
Crude liver extract therapy, intramuscularly, was begun at this time. She was given 2 cc. daily for a period of two weeks and then put on a dosage of 2 cc. twice a week. Associated with this there was a marked clinical improvement, with increased appetite and diminution of generalized malaise. Despite the fact that she had no further mercurial diuretics, she eliminated her oedema completely over a period of ten days. Her haemoglobin rose to the level of 12 g. Her initial reticulocyte count was 0.6 per cent. At no time during the liver therapy did she have a reticulocytosis higher than 1.2 per cent.

During the next three months she continued to improve steadily. Oedema disappeared entirely on complete bed-rest. Her appetite improved markedly so that she gained to a weight of 110 lbs. Her blood protein rose to 6.6 g. per cent with a reversal to normal of the albumin-globulin ratio. At this time she was allowed out of bed and encouraged to increase her activity. Attempts were made to give her whole liver by mouth and liver concentrates. These resulted in severe gastrointestinal upsets and had to be discontinued. She was returned to crude liver extract intramuscularly, given a total of 4 cc. weekly. After several more weeks of liver therapy she developed generalized urticaria after each injection, which became progressively severe, and the liver injections had to be discontinued. She received Brewer's yeast and thiamin chloride by mouth. At the present time she is on this regimen. Her dietary intake is adequate with a high vitamin content. Following extended walking she develops moderate ankle oedema which responds promptly to leg elevation. Her status at present is not as good as at the time she was getting intramuscular injections of liver despite the fact that her caloric and oral vitamin intake is adequate in all factors. The fault appears to be in her absorption through her intestinal mucous membrane.

This patient's gastrointestinal system was first investigated roentgenographically about three weeks after her admission. At that time, and in two subsequent series at approximately three-month intervals, hypermotility of the upper intestinal coils and a spastic filling defect of the lateral wall of the caecum were noted. The changes in the caecum were attributed to tuberculous ulceration with reflex hypermotility of the jejunum and proximal ileum. Review of the previously taken films showed hypermotility, abnormal segmentation, scattering effect, hypotonicity with loss of normal mucosal pattern (figures 1 and 2). Liver therapy was started with the dramatic results stated. It is to be noted and stressed that the therapeutic factor in the liver given was the B-complex and not the haemopoietic factor. This was manifested by a marked clinical improvement and a lack of reticulocytosis.

Case 2: H. F. White female, single, age twenty-seven. Occupation: housework.

This patient entered Cedarcrest on November 8, 1940 with the chief complaint of anorexia and cough of two months' duration. Her family, contact and past histories are essentially negative. Prior to onset of present illness her health had been fairly good. Two months prior to admission she noticed a rather acute onset of anorexia. During the following month she began to cough and occasionally raise sputum. At no time was there any blood spitting. For the two weeks prior to admission she frequently had fever and night-sweats. Greatest weight 115 lbs. seven months ago. Weight on admission 93 lbs.



FIGS. 1–6

On admission she was a well developed, malnourished girl of stated age in no acute distress. She ran a daily afternoon temperature elevation of 101°F. Positive physical findings were as follows: short, soft, nonreferred systolic murmur at the cardiac apex; increased tactile fremitus, impaired percussion note, bronchovesicular breath sounds and inspiratory crepitant râles over the left upper lobe, anteriorly and posteriorly. On admission the film of the chest showed a coalescent area of exudate accompanied by an annular shadow in the left first and second intercostal spaces. The admission diagnosis was pulmonary tuberculosis, left, far advanced.

No sputum was obtainable for examination on admission. Urine showed a very faint trace of albumin, but was otherwise negative. Her blood examination showed 10 g. haemoglobin with 4,400,000 erythrocytes, leucocytes 13,150 with 81 per cent polymorphonuclears (32 per cent nonlobulated, 49 per cent lobulated), 13 per cent lymphocytes, 5 per cent mononuclears, 1 per cent basophiles. The erythrocytes showed very slight anisocytosis and poikilocytosis. Sedimentation rate (modified Westergren) one hour 41 per cent; two hours 62 per cent. Kline exclusion test was negative.

Artificial pneumothorax was instituted on the left ten days after admission. Over a period of the first month the collapse, anatomically, appeared satisfactory although a distinct multilocular cavity was still present and several adhesions were visible extending from the apico-lateral border of the lung to the axillary portion of the thoracic wall. Throughout the next three months periodic pneumothorax refills were continued. She ran a low-grade temperature, intermittently raised positive sputum and did not appear to be progressing well.

During this period she began to complain of an intense anorexia, associated with feeling of fulness after small amounts of food and generalized vague abdominal discomfort. Gastric analysis showed an essentially normal acidity curve with numerous tubercle bacilli in the gastric juice. Gastrointestinal series done with fluoroscopic visualization but no detailed studies of the small intestines showed, at the time, small intestinal hypermotility. Subsequent review of the films gave only questionable indication of specific disease of the small intestines. The patient was given gastric sedatives and put on a bland multiple meal diet. The patient's complaints continued to be referred to her abdomen with continued anorexia, nonspecific abdominal pain and progressive nausea and vomiting. Two subsequent gastrointestinal series were interpreted as vagotonia, because of oesophageal and gastric spasm with much regurgitation. Review of these series show poor visualization of the small intestines, but definite segmentation, fragmentation and diminution in the height of the *valvulae conniventes*. Atropinization helped only slightly and intravenous fluids had to be resorted to for prolonged periods because of persistent vomiting.

At this time, following complaint of throat pain, examination showed early tuberculous pharyngeal and laryngeal involvement. She received butyn throat sprays, cauterization of the larynx and vocal rest was advised. Repeated chest examination showed extensive spread to the contralateral lung and, despite the fact that her exitus was expected, bilateral pneumothorax was instituted.

A repeat gastrointestinal series was done at this time, approximately one year after entry, with detailed studies of the small intestines. Changes in the small intestines were visualized which were interpreted as being definitely indicative of the B-complex deficiency picture (figures 3 and 4). The patient was started on 2 cc. of crude liver extract every other day, intramuscularly. Her response was very satisfactory and after six to eight injections her gastrointestinal complaints ceased almost entirely. She began to eat well, and for the first time since entrance in the sanatorium, progressive

weight increase was noted. With the marked improvement, the amount of injected liver was decreased to 2 cc. per week. This is being augmented by oral vitamin-B complex (Betalin compound, Lilly). Repeat gastrointestinal examination six weeks after the onset of liver therapy has shown a complete return to normal of her small intestinal pattern with only a slight residual hypermotility.

Serial haematological examinations have shown only a moderate improvement over her initial anaemia. Her general condition now is very much better than prior to liver and B-complex therapy. She has not, as yet, succeeded in stabilizing her pulmonary disease, but she has shown sufficient improvement so that with continued treatment we may expect a satisfactory end result.

Case 3: S. L. White female, single. Occupation: factory hand.

This patient was admitted on July 19, 1941, complaining of abdominal distress of three months' duration. Her family, contact, and past histories are negative except for a left-sided pleurisy four years prior to admission. At the onset of her complaints, which consisted of vague abdominal pain associated with intense anorexia she saw several physicians and the diagnosis of "nervous stomach" and "chronic appendicitis" was made. During a gastrointestinal series a chest lesion was discovered, although she never had any symptoms directly referable to pulmonary disease. She had lost 15 lbs. in an eight to ten month period.

On admission she was a pale chronically ill appearing girl of stated age in no acute distress. She ran a slight daily afternoon elevation. Pathological physical signs were limited to the chest where she gave indication of early disease in both apices. This was verified by X-ray examination and the admission diagnosis was moderately advanced pulmonary tuberculosis, bilateral. Sputum, concentrates and gastric contents were negative for tubercle bacilli. Urinalysis was essentially negative. Haemoglobin was 13 g., erythrocytes 4,640,000, leucocytes 12,150, polymorphonuclears 82 per cent (non-lobulated 20 per cent, lobulated 62 per cent), lymphocytes 13 per cent, mononuclears 5 per cent. Sedimentation rate 34 per cent.

Review of the films taken before entry gave indication of increasing fibrosis and it was felt that bed-rest and general sanatorium routine would be the best therapy. She received no specific treatment for a period of four months. Throughout this time there were no essential roentgenographic changes in her chest. The sedimentation rate remained accelerated and she showed intermittently positive sputa on serial examinations. It was felt that after this long bed-rest trial, her progress was not sufficiently satisfactory and artificial pneumothorax was attempted on the left, her more involved side. A free pleural space was not found and after several trials the attempts were discontinued. A left temporary phrenic paralysis was done about six months after admission. Shortly following this procedure there occurred evidently a perforation through a branch of the pulmonary artery and she developed a marked haematogenous dissemination with coalescence throughout both lung-fields. Her retrogression was now very rapid and she died seven months after admission. Autopsy permission was not obtained.

Throughout her hospital stay her primary complaint was referable to her abdomen. She complained almost continuously of vague abdominal pain, more intense in the right lower quadrant, associated with anorexia, nausea and frequent emesis. The first roentgenological investigation of her gastrointestinal tract resulted in a diagnosis of vagotonic stomach, upper intestinal hypermotility and colonic ptosis. This was a routine series without detailed studies of the small intestines. Because of her malnutrition and ab-

dominal complaints, she was put on a high vitamin, high caloric diet which was supplemented with tomato juice, codliver oil and thiamin chloride.

The patient continued to do poorly, and on two occasions her continued emesis was so severe that all foods by mouth had to be discontinued and continuous intravenous fluids resorted to. A repeat gastrointestinal study three months after admission with detailed studies of the small intestines resulted in the correct diagnosis of B-complex deficiency (figures 5 and 6). Crude liver extract, intramuscularly, was started immediately, 2 cc. every other day for a series of ten doses, and then continued on 4 cc. per week. This was supplemented by oral administration of B complex in adequate doses. Within one week following the onset of administration of this therapy, her abdominal complaints diminished markedly. Throughout the remainder of her life, with the exceptions noted below, she only had occasional abdominal distress. On two occasions the intramuscular injections of liver were discontinued while the oral intake, as outlined above, was continued. On both these occasions there was a marked and very rapid retrogression to her previous state, which promptly disappeared with the reinjection of liver. Here again, it was felt that the patient had faulty absorption because the intake and ability to utilize had both been verified and constant.

Despite the death of the patient by a complication that could not be anticipated nor adequately treated once it had occurred, it was felt that the parenteral injection of B complex had aided her markedly. A gastrointestinal series one week prior to her death showed a marked regression of the lesion in her upper intestinal tract, although hypermotility was still present. This was done at the time when the patient had already had her haematogenous spread and was acutely ill.

TECHNIQUE

The technique of the roentgenological examination of the small intestines is essentially that outlined by Buckstein (13). Two hundred g. of barium sulphate to approximately 600 cc. of water is ingested by mouth and observed fluoroscopically through the stomach and duodenum. With the onset of the passage of the opaque meal into the upper jejunal coils, Bucky films are taken and repeated every fifteen minutes for a period of from two to three hours. These are developed immediately and seen wet by the examiner. The interval between films is shortened or lengthened depending on the appearance of the small intestinal coils. With the exception of the first series done, the procedure is ordinarily stopped at the end of two to three hours with the beginning of the filling of the ascending colon.

A familiarity with the pattern of the normal small intestinal coils, of course, has to be secured before pathological abnormality can be diagnosed. Golden (11) describes the abnormality under the following headings: hypermotility, hypertonicity, hypomotility, hypotonicity (dilatation), abnormal segmentation, scattering effect and gas and fluid levels. Kantor (14, 15) has applied the term "moulage sign" to advanced instances where there is complete loss of the mucosal pattern, dilatation and almost invariably gas and fluid levels.

At this institution, during the year 1941, 56 gastrointestinal series were done on 39 patients. The full blown lesion, as described in the 3 patients reported, was found only in these 3 instances. These were all females. In 4 other patients a positive clinical story with associated upper intestinal hypermotility and dila-

tation without loss of the normal intestinal contour was found. These patients were all men. They were given B complex orally (Betalin compound, Lilly) in large dosages and all responded satisfactorily.

CONCLUSIONS

The lesion described is not common in the general run of tuberculosis sanatorium patients. We found it in only 17 per cent of those patients with sufficient gastrointestinal complaints to warrant roentgenological investigation. Included in the gross number of series done were 3 gastric carcinomata (all verified by operation and/or autopsy) and 2 peptic ulcers. Of the pathological findings in the gastrointestinal tract, however, this lesion is the most amenable to adequate therapy with a dramatic and hopeful effect. We feel that prior to the recognition of this lesion, the visualized changes would, if noticed, have been attributed to intestinal tuberculosis and treated as such. Inasmuch as the lesion is definite, and the treatment specific, we feel that adequate investigation should be employed before any of the vitamins or their isolated component parts be used for nonspecific abdominal complaints in tuberculosis, or elsewhere.

SUMMARY

The difficulty of definite diagnosis and adequate treatment of intestinal tuberculosis in the presence of pulmonary involvement is discussed. The usual site of the tuberculous lesion in the ascending colon has detracted from interest in visualization of the small intestines. A brief survey of the literature of the development of the description of the intestinal manifestations of vitamin-B-complex deficiency is given. Three cases with positive findings and associated pulmonary tuberculosis are discussed in detail. The technique of the study of the small intestine is detailed and the abnormal findings as described by previous investigators are recorded. A plea for adequate investigation and definite diagnosis before the institution of B-complex therapy is made.

SUMARIO

Discútese la dificultad que hay para hacer un diagnóstico bien definido y tratamiento adecuado en la tuberculosis intestinal cuando existe invasión pulmonar. La localización habitual de la lesión tuberculosa en el colon ascendente ha atenuado el interés en la visualización del intestino delgado. Ofrécese un breve repaso de la literatura relativa al desarrollo de manifestaciones intestinales cuando existe deficiencia de la vitamina compleja B. Discútense a fondo tres casos con hallazgos positivos y tuberculosis pulmonar asociada. Expónese la técnica del estudio del intestino delgado, y anótanse los hallazgos anormales que han descrito previos investigadores. Abógase por la investigación adecuada y el diagnóstico bien definido antes de iniciar la terapéutica con el complejo B.

Acknowledgment is made to Miss Marjorie Parker for the roentgenographs and photographic reproductions presented in this paper.

REFERENCES

(1) Brown, L., and Sampson, H. L.: Intestinal Tuberculosis, Diagnosis and Treatment, Lea and Febiger, Philadelphia, 1930.

(2) Goldberg, Benjamin: Clinical Tuberculosis, F. A. Davis Company, Philadelphia, 1939.

(3) Mackie, T. T.: Nontropical sprue, M. Clin. North America, 1933, *17*, 165.

(4) Mackie, T. T., Miller, D. K., and Rhoads, C. P.: Sprue: Roentgenologic changes in the small intestines, Am. J. Trop. Med., 1934, *15*, 671.

(5) Snell, A. M., and Camp, J. D.: Chronic idiopathic steatorrhea, Arch. Int. Med., 1934, *53*, 615.

(6) Golden, Ross: The small intestines and diarrhea, Am. J. Roentgenol., 1936, *36*, 892.

(7) Snell, A. M.: Clinical observation on nontropical sprue, South. M. J., 1935, *28*, 516.

(8) Hanes, F. M., and McBryde, A.: Identity of sprue, nontropical sprue, and celiac disease, Arch. Int. Med., 1936, *58*, 1.

(9) Mackie, T. T.: Vitamin deficiencies and the small intestine, J. A. M. A., 1941, *117*, 910.

(10) Golden, Ross: The small intestine in vitamin B deficiency, Ibid., 1941, *117*, 913.

(11) Lepore, M. J., and Golden, Ross: A syndrome due to deficiency of the vitamin B complex, Ibid., 1941, *117*, 918.

(12) Heublein, G. W., Thompson, W. D., and Scully, J. P.: The effect of a vitamin B complex deficiency on gastric emptying and small intestinal motility, Am. J. Roentgenol., 1941, *46*, 866.

(13) Buckstein, Jacob: Clinical Roentgenology of the Alimentary Tract, W. B. Saunders Company, Philadelphia, 1940.

(14) Kantor, J. L.: Roentgen diagnosis of idiopathic steatorrhea and allied conditions; practical value of the "moulage sign," Am. J. Roentgenol., 1939, *41*, 758.

(15) Kantor, J. L.: Further experience with the roentgen diagnosis of idiopathic steatorrhea, Arch. Int. Med., 1940, *65*, 988.

TUBERCLES AND FOREIGN-BODY GRANULOMATA[1]

Experiments in Mice and Guinea Pigs

WALTER PAGEL

In mice the tissue reaction to tuberculous infection differs substantially from that in other animals and man. The characteristic feature in mice is the absence of caseation, giant cells and tubercles. In their stead, however, is the formation of foam-cells and within them the acid-fast bacilli persist for a long time. When stained by Giemsa, the originally basophile rods become converted into eosinophile granules (Pagel, 1940). These phenomena suggest some relation to the high natural resistance of the mouse to tuberculosis. Is the peculiar tissue reaction of the mouse specific for infection with the tubercle bacillus or does it simply indicate an ability to treat tubercle bacilli as foreign bodies? Examination of this point may give some information on the origin and nature of the tubercle in general.

I. *The Effect of Heat-killed Tubercle Bacilli on the Tissues of the Mouse. Comparison with the Effect of Heat-killed and Live Bacilli in Guinea Pigs and Mice*

The tissue reaction to heat-killed tubercle bacilli has been extensively studied in guinea pigs and rabbits, but hardly ever examined in mice. Eighteen coloured mice were injected intracutaneously, each with approximately 100 million tubercle bacilli of the human type, killed by heating for one-half hour at 60°C. The site of inoculation was examined after three, six, eight and twelve days. Local necrosis and abscess formation was followed, from the sixth day, by accumulations of foam-cells. In 3 animals, instead of foam-cell nodules, diffuse infiltrations with mononuclear cells appeared. The foam-cells were full of acid-fast elements, chiefly granules which stained blue (basophile) with Giemsa.

The tissue reaction of the mouse to heat-killed tubercle bacilli is, therefore, identical with that to live bacilli in cytological detail. The fate of the bacilli, however, is different. Live bacilli are converted from basophile rods to eosinophile granules which is presumably connected with a loss in bacillary wax cover. This seems to take place in the foam-cells of the mouse (Pagel, 1940). No such changes were observed in heat-killed bacilli. It may be assumed that they are bound up with the digestion of the live microörganism. On the whole, heat-killed tubercle bacilli in the tissues of the mouse did not lend themselves to detection by Ziehl-Neelsen or Giemsa staining as easily as the live organisms. Whereas the latter could be seen regularly in the foam-cells up to a late stage (40 days), the heat-killed bacilli appeared after the sixth day only irregularly, were often faintly stained with Ziehl-Neelsen and showed up as weakly coloured granules or as a bluish haze in Giemsa preparations.

For comparison, 34 guinea pigs were inoculated intracutaneously with the

[1] From the Department of Pathology, Central Middlesex County Hospital, Acton Lane, London, N. W. 10, England.

same quantity of heat-killed tubercle bacilli as given to the mice and the sites of injection examined after two, three, five, six, seven, eight, nine, twelve, sixteen, eighteen and twenty-five days. From the sixth day, initial necrosis and abscesses were substituted by a diffuse mononuclear cell infiltration. In 3 animals some of the mononuclear cells were particularly large and had a foamy appearance, reminiscent of the foam-cells observed in mice. After the eleventh day mononuclear or epithelioid-cell nodules appeared regularly, being seen in 6 out of 11 animals as early as between the sixth and eleventh day. Giant cells of the Langhans type, occasionally found on the sixth and eighth day, became conspicuous after the twelfth day in about one-third of the animals.

Mononuclear and epithelioid cells were full of well preserved acid-fast organisms up to the sixteenth and eighteenth days. On the twenty-fifth day they either formed a fine granular, just visible, dust or had completely disappeared.

II. *Tissue Reaction to Heat-killed Tubercle Bacilli in Sensitized Mice and Guinea Pigs*

In 20 mice and 20 guinea pigs the response to *repeated* intracutaneous inoculation with heat-killed tubercle bacilli was examined and compared with the result of the first inoculation. This preceded by, at least six weeks, the second inoculation, the third by eight weeks and the fourth by ten weeks. In addition, 15 guinea pigs received a course of 8 intraperitoneal injections of 1 mg. heat-killed tubercle bacilli at weekly intervals. When tuberculin sensitive, these animals were inoculated with heat-killed tubercle bacilli intracutaneously in the same way as the other guinea pigs.

The result may be summarized as follows:

1: No differences were seen between the tissue response of the mouse to first and repeated inoculation of heat-killed tubercle bacilli.

2: In guinea pigs, the fate of the inoculated bacilli differed substantially in the first and repeated inoculations. Bacilli of the first injection disappeared from the tissue between the twentieth and twenty-fifth day, those of repeated inoculation, however, much earlier, that is, between the eighth and fourteenth day (figures 1 and 2). The cells of the allergic animals often contained acid-fast droplets, obviously remnants of the destroyed bacillary material which had become confluent (figure 3).

3: This speedy digestion of the organisms in the allergic animal was in no way connected with a tissue response different from that of the normergic guinea pig. In both groups of animals mononuclear cell infiltration and nodules were encountered from the sixth day onward, yet abundant bacilli appeared in the cells of the nodules after first inoculation and no bacillary material after repeated inoculation.

4: Giant cells, quite commonly observed in normergic animals, were only exceptionally seen after inoculation in those animals which had been vaccinated with heat-killed tubercle bacilli intraperitoneally. In these animals nodules consisting of small epithelioid cells, developed early at the site of intracutaneous injection of heat-killed tubercle bacilli, in contrast with the large mononuclear and giant cells seen in normergic animals.

Thus, the cellular response to inoculation of heat-killed tubercle bacilli showed no substantial differences after first and repeated intracutaneous administration. In this respect the guinea pig behaves just the same as the mouse. The response

of the guinea pig, however, differs substantially from that of the mouse as far as the fate of the inoculated bacilli in normergic and allergic tissue is concerned.

III. *Tissue Reaction of Mice and Guinea Pigs to Organisms Other than Tubercle Bacilli*

The following organisms were used:

(a) *B. coli*, isolated from faeces.
(b) Haemolytic streptococci, isolated from pleural pus.
(c) Pneumococci, isolated from sputum of a patient with lobar pneumonia.
(d) Diphtheroid bacilli from vaginal secretion.

Approximately 100 million organisms—live as well as heat-killed (one-half hour at 60°C.)—were inoculated intracutaneously and the sites of inoculation examined histologically at various intervals.

(a) *B. coli:* Intracutaneous injection of *B. coli* was followed, in 20 mice, by necrosis and abscess formation which, in some animals, remained conspicuous up to the fourteenth day, that is, the last day of examination. Mononuclear cell infiltration and foam-cells appeared from the sixth day, mostly in the periphery of the initial necrosis or abscess (figure 4). Organisms, numerous in the latter, were invisible in the mononuclear and foam-cells.

The tissue reaction is, therefore, identical in principle with that to tubercle bacilli. Abscess and necrosis were more conspicuous in *B. coli* infection, mononuclear and foam-cell infiltration in tuberculous infection. Only quantitative differences were observed between the reaction to live and heat-killed *B. coli*. Repeated inoculation of *B. coli* elicited a typical Arthus phenomenon in some animals.

In the guinea pig the initial abscess was followed by mononuclear cell infiltration from the sixth day and mononuclear-cell nodules from the eighth day; the nodules were conspicuous and contained giant cells of the Langhans type in the majority of the 30 guinea pigs examined (figure 5). Repeated injection elicited a hypersensitive response in some animals without influencing the histological changes substantially. All tissue changes were more extensive and pronounced when live bacilli had been inoculated. No qualitative differences were therefore extant between the tissue reaction of the guinea pig to *B. coli* and tubercle bacilli.

(b) and (c) *Streptococci and pneumococci:* In 8 mice as well as twenty-two guinea pigs the effect of these organisms was almost identical with that of *B. coli* (figures 6 and 7). In the guinea pigs, formation of mononuclear-cell nodules was even more conspicuous than after inoculation of *B. coli* and appeared occasionally as early as on the sixth day. Abscess and necrosis were more pronounced when live organisms were used, but no differences between the effect of live and dead cocci were observed in the formation of nodules and giant cells of the Langhans type. Organisms, numerous in the initial abscess, were invisible in the tubercles and giant cells.

(d) *Diphtheroid bacilli:* In 10 mice foam-cells predominated from the seventh

day after inoculation in the periphery of the initial changes. In the 18 guinea pigs examined, abscess and necrosis, hardly visible after three days, were soon substituted by extensive mononuclear cell infiltrations (fifth day) in which nodules and giant cells of the Langhans type became conspicuous from the ninth day. The effect of heat-killed organisms almost equalled that of the living bacilli. Mononuclear and giant cells were particularly big and well formed in the experiment with the diphtheroid bacilli. Peculiar basophile bands and crystals but no organisms were visible in their protoplasmatic bodies (figure 8).

Thus, in mice as well as in guinea pigs, the tuberculous tissue response is non-specific as far as histological detail, such as the formation of foam-cells and mononuclear-cell nodules, respectively, is concerned.

IV. *The Response to Foreign Bodies in Mice and Guinea Pigs*

These results suggest that a foreign body effect accounts for the uniform tissue reaction after inoculation of so many different microörganisms. The typical tissue response to foreign material, that is, foreign-body giant cells and tuberculoid granulomata, however, had been observed in guinea pigs only. Are mice unable to form tubercles, or is the character of the foreign material used (organisms) responsible for the lack in tubercle formation and for the peculiar changes such as foam-cell nodules? To answer this question 0.2 cc. of (*a*) seal oil, (*b*) olive oil, (*c*) of a milky suspension of ground cover slips and (*d*) óf pure calcium carbonate were injected intracutaneously in 10 guinea pigs and 10 mice and the sites of injection examined at various intervals.

In response to all these irritants the mouse formed tuberculoid granulomata which were rich in giant cells (figure 9). The reaction differed in no way from that of the guinea pig to the same irritants. None of the elements characteristic

---

Fig. 1. (Top left.) Site of intracutaneous inoculation of heat-killed tubercle bacilli in a normergic guinea pig after twelve days. Macrophages filled with acid-fast rods.

Fig. 2. (Top center.) The same in a guinea pig after repeated inoculation. Same magnification. Hardly any acid-fast material left in the macrophages, but cytological detail of tissue response identical with that observed in the normergic guinea pig.

Fig. 3. (Top right.) Acid-fast droplets as remnants of the inoculated bacilli. Site of intracutaneous injection in an allergic guinea pig after twelve days. Ziehl-Neelsen preparation.

Fig. 4. (Middle row left.) Site of intracutaneous inoculation of *B. coli* in a mouse after six days. Extensive foam-cell proliferation.

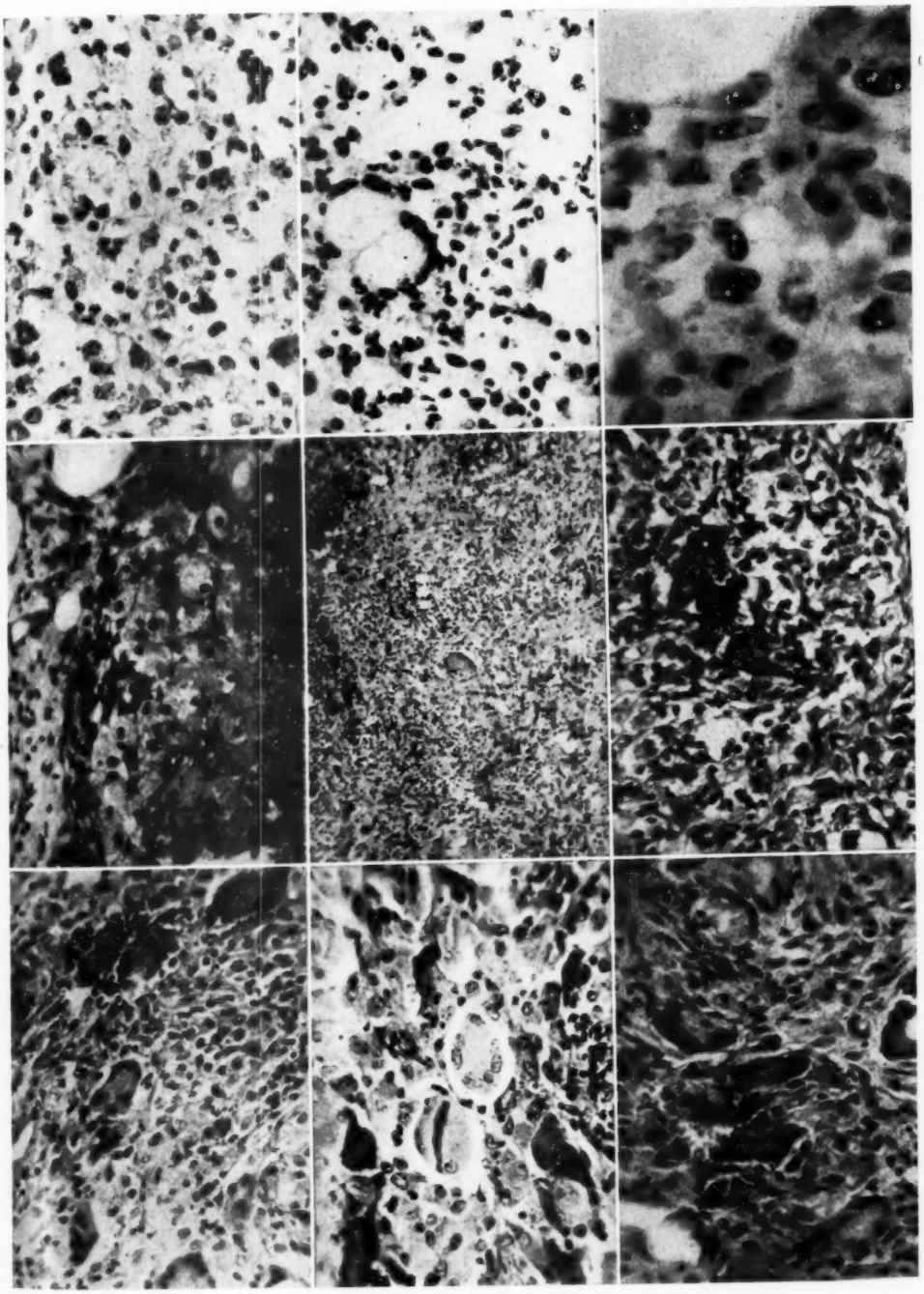
Fig. 5. (Middle row center.) The same in a guinea pig after eighteen days. Epithelioid-cell nodule with giant cells of the Langhans type.

Fig. 6. (Middle row right.) Site of intracutaneous inoculation of live streptococci in a guinea pig after fourteen days. Mononuclear-cell nodule with giant cells of the Langhans type.

Fig. 7. (Bottom left.) Numerous giant cells of the Langhans type at the site of intracutaneous inoculation of live pneumococci in a guinea pig after seventeen days.

Fig. 8. (Bottom center.) Peculiar large giant cells at the site of intracutaneous inoculation of live diphtheroid bacilli in a guinea pig after nine days.

Fig. 9. (Bottom right.) Large giant cells of the Langhans type seventeen days after intracutaneous injection of a milky suspension of calcium carbonate in a mouse.



FIGS. 1–9

of the response of the mouse to microörganisms (including tubercle bacilli) appeared.

Mouse tissue seems, therefore, to be able to distinguish microörganisms and other foreign material, whereas the guinea pig reacts in a uniform manner to both. Formation of foam-cells is not the typical tissue response of the mouse to foreign material. The mouse is able to form giant cells and tuberculoid nodules but fails to do so in response to inoculation of organisms.

DISCUSSION

Microörganisms as causes of tuberculoid granulomata have been but rarely mentioned in experimental pathology. Blumenberg (1925) compared the dermal tissue response to 0.1 mg. *B. coli* and Old Tuberculin in tuberculous patients and normal volunteers. He discovered in both the identical picture of epithelioid-cell nodules with scanty giant cells. After fifty days the changes were slightly less marked in the response to *B. coli*, but identical in quality with the changes elicited by tuberculin. Once, however, saline injection had caused similar changes in a normal man, which was regarded as a reaction to small foreign bodies suspended in saline. The present author has examined the site of intracutaneous saline injections in 12 guinea pigs and 10 mice at various intervals up to twenty days and never found more than a trivial accumulation of leuco- and lymphocytes up to the fifth day. Kettle (1927) noticed that streptococci, isolated from patients with puerperal septicaemia or cellulitis, and diphtheria bacilli provoked not more than small, healing abscesses in the subcutis of mice. Bacillary suspensions may therefore act as harmless foreign substances and elicit in guinea pigs a tissue reaction indistinguishable from the ordinary foreign-body response. The reaction in the mouse, however, proves that microörganisms do not act altogether in the same way as ordinary foreign material. The administration of corpuscular material, such as ground glass, calcium carbonate or oil, causes typical granulomata with Langhans giant cells. These are absent when microörganisms are injected and foam-cells appear in their stead. These correspond to the cells of the classical tubercle, as our observations in guinea pigs show where in some instances, after inoculation of heat-killed tubercle bacilli, foam-cells were seen mixed with mononuclear and epithelioid cells. Nevertheless the foam-cell is characteristic in itself and should be regarded as a special entity. This is borne out by their complete failure, in contrast to ordinary mononuclear and epithelioid cells, to develop into giant cells. Digestion and elimination of injected organisms seem to be the chief functions of the nodules described in the present experiments. This is borne out by the tubercle bacilli seen in the cells which constitute the granuloma up to a late stage. When bacteria other than the tubercle bacilli were used, however, no organisms could be observed in the cells of the granuloma. Moreover, in sensitized animals, tubercle bacilli rapidly disappeared from the site of inoculation, yet the histological changes were identical with those in normergic animals in which bacillary digestion was slow. There was no evidence of earlier develop-

ment of nodules after repeated intracutaneous inoculation which could account for the speedy disappearance of the organisms in them. Properties acquired by the cells during sensitization, rather than the presence of the cells as such, may therefore account for the rapid digestion of tubercle bacilli in sensitized animals. Nor could evidence be adduced for a rôle of allergy in the formation of giant cells. After intracutaneous inoculation of heat-killed bacilli, giant cells were abundant in normal, but absent in vaccinated animals. It may be assumed that these cells are the response to foreign-body action of the organisms which was more pronounced in the normal than in the sensitized animals, since the bacillary bodies disappeared more quickly from the tissue of the latter, as we have shown.

In mice the rôle of allergy and specificity was less impressive than in guinea pigs. Formation of foam-cells is certainly no privilege of tuberculous infection. Other features such as the absence of caseation, the slow spread of bacilli from the site of inoculation, their long persistence and morphological changes in the foam-cells seem to be characteristic of the tuberculous tissue response in mice and may be connected with the high natural resistance of this animal to tuberculous infection. It enables them to treat tubercle bacilli just as any bacillary foreign material and thereby to keep infection restricted to the site of inoculation at least for a long period.

In the present experiments, foreign-body action as the cause of tubercle formation has been brought to the foreground. No material specific to one group of organisms, such as the lipoid constituents of acid-fast bacilli, seems to be a requisite essential in the formation of tuberculoid granulomata. Yet, it is not pure foreign-body action which is responsible for the tissue reaction under discussion. Wurm (1930) has shown that thin sheets of glass such as coverslips or strips of celloidin introduced into a subcutaneous pouch will become surrounded by a layer of large plasmodia—the typical foreign body giant cells—which are due to the surface action of the foreign body preventing the cells from division, but he has never seen granulomata or tubercles in these experiments. The "foreign body" as such elicits by its mechanical and surface action the typical foreign-body giant cell and nothing else; "foreign material," however, in which a certain chemical effect is added, will provoke granulomata indistinguishable from tubercles with all intermediate forms of giant cells between the Langhans and foreign-body type. The tubercle, such as observed in infectious diseases and under experimental conditions, is therefore the expression of the ability of the tissue to treat any irritant as "foreign material." The irritant need not be an organism such as the typhoid bacillus or *Brucella*. It may be an unorganized antigen such as horse serum which, as Roulet (1931) has shown, causes trivial changes during its penetration into the tissues of a normergic animal, but elicits tubercles when its passage through sensitized tissues is prevented or retarded. In these areas allergy accounts for its treatment as corpuscular and unabsorbable foreign material. In tuberculosis, action of the bacillary phosphatides (Rich and McCordock (1929), Sabin *et al.* (1930)) explains the formation of many, but certainly not all tubercles. The ability of the

tissue to treat the bacillus or any other irritant as "foreign material," to arrest it, to retard its absorption, to wall it off, may account for the tubercle formation even in tuberculosis.

SUMMARY AND CONCLUSIONS

1. Heat-killed tubercle bacilli elicit in mice the same tissue response as live tubercle bacilli. Conversion of basophile bacillary rods into eosinophile granules occurring in the foam-cells of the mouse inoculated with live tubercle bacilli was not seen with heat-killed organisms.

2. In mice specific sensitization in no way modified the tissue response to inoculation with heat-killed tubercle bacilli; in guinea pigs it accounted for speedy intracellular digestion of the organism with the absence of giant cells. The speed of bacillary digestion was independent of the quality of the tissue reaction.

3. Various microörganisms other than tubercle bacilli caused in mice and guinea pigs a response identical with that to inoculation with tubercle bacilli in some histological detail (foam-cell and tuberculoid granulomata, respectively).

4. Mice, unable to form giant cells and tuberculoid granulomata after inoculation of organisms, do so after injection of classical foreign bodies such as ground cover slips, calcium carbonate or oil. To these irritants the tissue response of the mouse is identical with that of the guinea pig. To microörganisms the tissue response of the mouse is different from that of the guinea pig.

5. The peculiar tissue response of mice to the tubercle bacillus is, therefore, neither specific nor due to an inability of this animal to form tubercles.

6. The ability of the tissue to treat irritants, including the tubercle bacillus, as "foreign material" may account for tubercle formation in some instances, even in tuberculous infection.

SUMARIO Y CONCLUSIONES

1. Bacilos tuberculosos matados al calor provocan en los ratones la misma respuesta histológica que los vivos. Con los microbios destruídos al calor no se observó la conversión de bastoncillos basófilos en gránulos eosinófilos que tiene lugar en las células espumosas del ratón inoculado con bacilos tuberculosos vivos.

2. En los ratones la sensibilización específica no modificó en forma alguna la respuesta histológica a la inoculación de bacilos tuberculosos muertos al calor; en los cobayos explicó la rápida digestión intracelular del microbio con falta de células gigantes. La celeridad de la digestión bacilar fué independiente de la forma que tomó la reacción histológica.

3. Varios microbios distintos de los bacilos tuberculosos provocaron en los ratones y cobayos una respuesta idéntica a la producida por la inoculación de bacilos tuberculosos en algún detalle histológico (células espumosas y granulomas tuberculoideos, respectivamente).

4. Los ratones incapaces de formar células gigantes y granulomas tuberculoideas después de inocularles los microbios, pueden formarlos después de inyectarles cuerpos extraños clásicos, tales como cubreobjetos triturados, carbonato de

calcio o aceite. A estas sustancias irritantes la respuesta histológica del ratón es idéntica a la del cobayo, mientras que es distinta a los microbios.

5. La peculiar reacción histológica de los ratones al bacilo tuberculoso no es, por lo tanto, ni específica ni debida a incapacidad de ese animal para formar tubérculos.

6. La capacidad del tejido para tratar como materias extrañas las sustancias irritantes, incluso el bacilo tuberculoso, puede explicar la tuberculogenia en algunos casos, y hasta en la infección tuberculosa.

The author wishes to acknowledge his gratitude to Dr. R. G. Bannerman for reviewing the manuscript and to Mr. F. B. Trenholme and Mr. J. E. Mayhew for technical assistance.

REFERENCES

(1) Blumenberg, W.: Beitr. z. Klin. d. Tuberk., 1925, *61*, 509.
(2) Kettle, E. H.: Lancet, 1927, *1*, 1169.
(3) Pagel, W.: Am. Rev. Tuberc., 1940, *42*, 58.
(4) Rich, A. R., and McCordock, H. A.: Bull. Johns Hopkins Hosp., 1929, *44*, 237.
(5) Roulet, F.: Verhandl. d deutsch. pathol. Gesellsch., 1931, *26*, 189.
(6) Sabin, F., Doan, C. A., and Forkner, E. F.: J. Exper. Med., 1930, *52*, Suppl. 3.
(7) Wurm, H.: Beitr. z. path. Anat., 1930, *85*, 401.

EXPERIMENTAL TUBERCULOSIS IN HYPERGLYCAEMIC ALBINO RATS[1, 2]

M. MAXIM STEINBACH AND CHARLES J. DUCA

Tuberculosis has been considered a frequent and serious complication in the human diabetic and this view is substantiated by clinical, roentgenological and pathological observations. However, many workers have felt that the two diseases are not necessarily related. In 1912, Montgomery (1) came to the conclusion that there was no difference in the incidence of tuberculosis among diabetics and the general population. In recent times many clinicians (Joslin (2), Grafe (3), and others) have adhered to this view. On the other hand, other competent observers believe that the diabetic is constantly menaced by tuberculosis. Banyai (4) reported the incidence of tuberculosis in diabetics as 2.6 per cent or three times as great as in the general population. Root's (5) splendid work has confirmed this opinion. European observers give the incidence of tuberculosis in diabetics as from 2 per cent (Ruiz (6)) to 10 per cent (Vrhovac (7)).

The course of tuberculosis in the diabetic, as well as that of other infections, is undoubtedly very severe when the diabetes is uncontrolled. Moreover, many workers have stated that tuberculosis still remains somewhat invasive even when the diabetes is carefully controlled (Thiery (8), Jeanneret (9), Derschied and Toussaint (10)). On the other hand, Joslin (2), Wiener and Kavee (11) and others feel that tuberculosis is no worse in the controlled diabetic than in the nondiabetic individual. It is obvious that there has been no convincing solution of the problem of the relationship of diabetes to tuberculosis.

Whether the diabetic is or is not more susceptible to tuberculosis is an important public health and clinical problem. The solution of this problem has almost always been attempted by statistical or clinical studies. The inaccuracies and errors which should be rigidly excluded from such studies have been well discussed by King (12). King concluded that tuberculosis is still about five times more frequent in diabetics than in the general population and urged that this fact should receive more general recognition. Perla and Marmorsten (13) point out that many cases of early tuberculosis in the diabetic are overlooked and adequate treatment is therefore neglected.

Because of the difficulty in forming an opinion from clinical or statistical studies, we have long felt that an experimental approach could more adequately cope with this problem. The relationship of diabetes mellitus to resistance to tuberculosis has been studied previously to some extent on an experimental basis (14, 15), and the work reported here is an extension of this previous investigation.

[1] From the Department of Bacteriology, Columbia University College of Physicians and Surgeons, New York, New York.

[2] Supported by a grant from the National Tuberculosis Association.

INTRODUCTION TO EXPERIMENTS

There is no ideal way of producing diabetes in the experimental animal except by complete extirpation of the pancreas. Originally we experimented with cats and ferrets, but in these animals the duration of life following pancreatectomy was so short that we could not observe the progress of tuberculous disease. We then learned that according to Young (16) the injection of fresh anterior pituitary gland suspension would produce diabetes in dogs. We tried this method in a large number of dogs, but abandoned the experiment because: (*1*) many dogs died of peritonitis, as it was almost impossible to render the injected material sterile; (*2*) such animals as became diabetic required constantly increasing doses of pituitary to maintain hyperglycaemia.

We thereupon decided to adapt Young's method of experiments upon rats which had previously been pancreatectomized. Following this method, the pituitary glands were frozen in dry ice within one hour of removal from the oxen and kept in this state until they were decapsulated. The anterior portion was then removed and ground with chilled sterile sand and physiological saline. The ground mixture was let stand in the refrigerator at 6°C. for one hour and was then centrifuged at low speed while cold. The thick supernatant fluid was removed and kept in the refrigerator until just before use. Throughout this work, no extract older than three days was used.

Experiment I: Fifty albino rats, twenty-five days of age, were pancreatectomized as completely as possible and were at once placed on a diet which included 40 per cent sucrose by weight, with adequate amounts of essential foods and extra quantities of vitamins A, B and D. The fasting blood sugars of the experimental animals were determined every two weeks, by the Schaffer-Hartman-Somogyi micromethod. As controls, the fasting blood sugars of 10 normal albino rats (thirty days of age) were determined by the same method, and found to average 95 mg. per 100 cc., ranging from 70 to 116. On the day after pancreatectomy, the experimental animals were started on daily intraperitoneal injections of crude extract of anterior pituitary, the initial dosage of 0.5 cc. being increased daily by 0.5 cc., until 3 cc. were being given daily. This dose was continued during the course of the experiment. Seven days after pancreatectomy, the rats were infected intravenously with 1 mg. of pathogenic bovine tubercle bacilli (B1).

Because of the daily injection of relatively large amounts of crude extract, almost every rat developed peritonitis, and many died from this cause. No animal that survived less than twenty-five days after infection is included in this report. This left 21 rats which were divided into two groups: 10 rats having blood sugars of over 140 mg., averaging 158, and 11 rats having fasting blood sugars under 140 mg., averaging 124. Five control rats, infected with an equal dose of bacilli by the same route, but not pancreatectomized, were studied at the same time. These were permitted to survive a week longer than the last of the treated animals. The results of the experiment are summarized in table 1.

It is seen that the fasting blood sugars of the different groups are about 30

mg. apart and the amount of tuberculosis increases with the rise in the blood sugar. Microscopical study of the tissues confirmed the autopsy findings and showed the tubercles to be composed mainly of monocytes, with a few lymphocytes and occasionally epithelioid cells. Sometimes the monocytes had fused to form multinucleated cells and in a few cases central necrosis in the tubercle was observed. In the control rats, the tubercles were of the same pattern, but no caseation was seen. It was of interest to note that the tubercles of the hyperglycaemic animals contained many more bacilli than were found in the controls.

Experiment II: We thought it of interest to determine whether any one part of the treatment was responsible for the increased amount of tuberculosis found

TABLE 1

GROUP	NUMBER OF ANIMALS	AVERAGE DAYS AFTER INFECTION	AVERAGE FASTING BLOOD SUGAR	AVERAGE AMOUNT OF TUBERCULOSIS AT AUTOPSY				
				Lungs	Liver	Spleen	Lymph nodes	Summary
Moderate hyperglycaemia.....	10	72	158	2.9+	1.7+	0.8+	0.6+	2.2+
Slight hyperglycaemia.....	11	40	124	1.5+	1.1+	0.3+	0.6+	1.1+
Controls.....	5	80	95	0.5+	0	0	0	0.5+

(Amount of tuberculosis graded from 0 to 4+.)

TABLE 2

GROUP	NUMBER OF ANIMALS	DAYS AFTER INFECTION	FASTING BLOOD SUGAR	AMOUNT OF TUBERCULOSIS AT AUTOPSY				
				Lungs	Liver	Spleen	Lymph nodes	Summary
I	5	60	154	2.8+	2.2+	1.6+	0	2.1+
II	5	50	156	2.4+	1.8+	1.2+	0.6+	2.0+
III	7	82	147	2.6+	0	0	0	2.0+
IV	5	82	135	2.2+	0	0	0	1.5+
V	5	95	97	1.0+	0	0	0	1.0+

in the hyperglycaemic rats. The experiment was therefore repeated, with some variations.

Fifty albino rats, twenty-five days of age, were divided into 5 groups and were treated as follows:

Group I: As in experiment I—pancreatectomy, anterior pituitary injections and high carbohydrate diet.
Group II: Pancreatectomy, anterior pituitary injections, normal diet.
Group III: Pancreatectomy, high carbohydrate diet.
Group IV: Subcutaneous injection of 20 per cent glucose solution twice daily, normal diet.
Group V: Controls.

Operation and infection were the same as in experiment I. Applying the same standards as in experiment I, about half of the original number of animals

qualify for inclusion in the series reported. The findings at autopsy are shown in table 2.

Microscopical examination of sections taken at autopsy confirmed the gross findings. Although no caseation was encountered, in the main the differences found in experiment I were present here. Microscopically, the lesions of the first four groups were essentially the same and differed from group V in that they contained larger numbers of acid-fast bacilli. The spread of tuberculosis to abdominal organs occurred only in groups I and II, which received intraperitoneal injections of anterior pituitary extract. It is possible that the trauma incident to this procedure lowered resistance locally. It may also be noted that the anterior pituitary injections appear to have had relatively little influence on the blood sugar level. That pancreatectomy in the albino rat, *per se*, does not produce hyperglycaemia, we have previously demonstrated by a series of basic preliminary experiments (not published). Pancreatectomy, however, produces a lowered sugar tolerance. When such an animal is given a high carbohydrate diet or fresh anterior pituitary extract, hyperglycaemia results.

DISCUSSION

Our results indicate that the rat becomes more susceptible to induced tuberculous infection when rendered hyperglycaemic. One cannot say that the hyperglycaemia is the sole cause of this change in resistance. Changes in carbohydrate metabolism are accompanied by many other changes in body functions. Long (17) has offered an ingenious explanation which links the increased susceptibility of the diabetic with his increased fat breakdown and a concomitant increase in glycerol. Other factors which are present in the diabetic individual are the accumulation of lipids, inability to utilize vitamins and disturbances of other endocrine glands due to the interrelationships among these organs. We are at present carrying out experiments in diabetic dogs in an attempt to ascertain the factors, other than hyperglycaemia, causing the lowered resistance to infection in the diabetic.

SUMMARY

The natural resistance of the rat is apparently lowered by induced hyperglycaemia, as demonstrated in both of our experiments. Tuberculosis developed more extensively in the hyperglycaemic rat. The tubercles were conglomerate and more wide-spread, and, of greatest interest, they contained many more acid-fast bacilli than those of the controls. Although the hyperglycaemia in these rats was mild in character, it apparently rendered the rat more susceptible to experimental tuberculosis.

SUMARIO

La resistencia natural de la rata es aparentemente aminorada por una hiperglucemia provocada, según se demostró en dos experimentos. La tuberculosis revistió más extensión en la rata hiperglucémica. Los tubérculos eran más conglomerados y difundidos, y, lo que es de mayor interés, contenían muchos

más bacilos ácidorresistentes que los de los testigos. Aunque en estas ratas la hiperglucemia era leve, al parecer susceptibilizó a estos animales a la tuberculosis experimental.

REFERENCES

(1) MONTGOMERY, C. M.: Am. J. M. Sc., 1912, *144*, 543.
(2) JOSLIN, E. P.: Treatment of Diabetes, 4th ed., Lea and Febiger, Philadelphia, 1928.
(3) GRAFE, E.: Metabolic Diseases and Their Treatment, Lea and Febiger, Philadelphia, 1933.
(4) BANYAI, A. L.: Am. Rev. Tuberc. 1931, *24*, 650.
(5) ROOT, H. F.: New England J. Med., 1934, *210*, 1.
(6) RUIZ, V.: Rev. espan. Tuberc., 1935, *52*, 819.
(7) VRHOVAC, V.: Lijecnicki Vjesink, 1937, *59*, 205. Abstracted in Presse méd., Rev. des J., 1937, *45*, 168.
(8) THIERY, J. E.: Tuberculose pulmonaire et diabete, Vol. I, Jouve, Paris, 1934.
(9) JEANNERET, R.: Schweiz. med. Wchnschr., 1940, *70*, 531.
(10) DERSCHIED, G., AND TOUSSAINT, P.: Rev. belge tuberc., 1939, *30*, 333.
(11) WIENER, J. J., AND KAVEE, J.: Am. Rev. Tuberc., 1934, *30*, 181.
(12) KING, S. E.: Quart. Bull. Sea View Hosp., 1936, *1*, 416.
(13) PERLA, D., AND MARMORSTEN, J.: Natural Resistance and Clinical Medicine; Little, Brown, & Co., Boston, 1941.
(14) STEINBACH, M. M., AND DESKOWITZ, M.: Proc. Soc. Exper. Biol. & Med., 1933, *30*, 1053.
(15) STEINBACH, M. M., KLEIN, S. J., AND DESKOWITZ, M.: Am. Rev. Tuberc. 1935, *32*, 665.
(16) YOUNG, F. G.: Lancet, 1937, *2*, 372.
(17) LONG, E. R.: Arch. Path., 1928, *6*, 1138.

CONGENITAL TUBERCULIN HYPERSENSITIVENESS AND SPECIFIC TUBERCULO-ALLERGIC IMMUNITY[1,2]

H. J. CORPER AND C. CLARK

In an analysis of the tubercle bacillus and its natural products, derived from growth on a simple synthetic non protein medium, it was found that maximum bacillary growth of human tubercle bacilli occurs within two to three months, while tuberculoprotein liberation into the medium takes place mainly after maximum growth has been attained. It was noted also that the bacillary body sensitizes primarily to tuberculo-allergy and serves to immunize against virulent infection, while the natural filtrate, containing tuberculoprotein, sensitizes to anaphylaxis, provokes anaphylactic shock and allergic intoxication, but does not sensitize to allergy nor specifically immunize against virulent infection (1). Tuberculo-anaphylaxis, tuberculo-allergy and tuberculo-immunity show distinctive characteristics which lead to the conclusion that they are separate and apparently unrelated biological phenomena (2). In further elaboration of these findings (3), it was noted that relatively small amounts of filtrate (tuberculoprotein) obtained from the growth of tubercle bacilli on synthetic non protein media are required to sensitize and intoxicate normal guinea pigs anaphylactically. Such filtrates will not sensitize to a positive skin (tuberculoprotein) reaction (skin allergy). After an appropriate incubation period, bacilli-sensitized or tuberculous animals do not respond to an injection of filtrate by an acute anaphylactic shock reaction; but they do reveal a protracted (allergic) intoxication to a suitable amount of filtrate with fatal issue after one to three days, except when the tuberculous involvement is very marked. Filtrate-sensitized guinea pigs do not develop an acute (anaphylactic) shock after the injection of washed tubercle bacilli, while bacilli-sensitized and tuberculous (allergic) animals succumb to these injections. The filtrate (anaphylactic) sensitization can be transferred passively by means of blood from about 45 per cent of the donors, while the bacillary and tuberculous (allergic) principles are never transferrable passively to normal recipients. The lethal effect (allergic) of filtrate in tuberculous animals appears to depend upon the time and amount of involvement following infection with virulent tubercle bacilli. The skin (allergic) reaction may be entirely absent in guinea pigs which still retain their specific tuberculosis immunity, and *vice versa*. Desensitization with filtrate (tuberculoprotein) to the skin (tuberculin) reaction exerts no influence upon the specific tuberculosis immunity. Guinea pigs sensitized with filtrate do not lose this anaphylactic sensitivity upon infection with virulent human tubercle bacilli and injection of bacillary suspension of avirulent human tubercle bacilli (4). The two reactions (anaphylactic and allergic) can be demonstrated to coexist in the same animal when recovery from the anaphlactic reaction occurs and subsequent protracted allergic death results later. It was concluded that specific anaphylaxis plays no significant

[1] From the Research Department of the National Jewish Hospital, Denver, Colorado.
[2] This study was aided by the Jacques Labarrere Fund for Tuberculosis Research.

rôle in experimental tuberculosis while the intoxication is closely related to specific allergy whether due to tuberculin or bacillary body, although some of the details of the latter action are not fully understood.

Since most of the early literature on these subjects either did not differentiate tuberculo-anaphylaxis from tuberculo-allergy satisfactorily or proved insufficiently conclusive for drawing satisfactory deductions, and were reviewed adequately in previous articles, they will not be cited again. It suffices to say that so far as the available literature is concerned, there are no differential data on the hereditary transfer of tuberculo-anaphylaxis and tuberculo-allergy. Since our studies showed that tuberculo-anaphylactic hypersensitiveness can be transferred in a fairly high percentage from the donor to a normal recipient with the blood (or citrated plasma) but that tuberculo-allergic hypersensitiveness cannot be transferred, it appeared desirable to determine whether the hypersensitiveness would pass from mother to offspring and the conditions under which this occurs. For the purpose of determining the mother-offspring passage, the following experiments were performed on guinea pigs.

MOTHER TO OFFSPRING PASSAGE OF TUBERCULO-ANAPHYLACTIC HYPERSENSITIVENESS

The passage of tuberculoprotein hypersensitiveness was studied by giving female guinea pigs a single intravenous (ear vein) injection of the bacteria-free filtrate from growing human tubercle bacilli on a synthetic nonprotein medium (Wong-Weinzirl (5)). The equivalent of about 10 mg. tuberculoprotein as filtrate was given each mother guinea pig intravenously. The cultures from which the filtrate was prepared usually were about six to nine months old (maintained at 37°C. during this entire time). The tuberculoprotein content was determined by trichloracetic acid precipitation according to Seibert (6). In the first experiment with offspring, 4 mothers delivered viable young for the purpose of this study.

Mother #1 had a young born two months after the tuberculoprotein injection intravenously (20 cc. filtrate containing 12.8 mg.). When this offspring was two months old, an intravenous injection of 4 cc. of filtrate containing about 2.2 mg. tuberculoprotein was given which resulted in a lethal acute anaphylactic shock within a few minutes.

Mother #2, also given an intravenous injection of filtrate containing 12.8 mg. tuberculoprotein, delivered twins three months after the injection. One of the young lived and at two months of age was given 2.5 cc. filtrate (1.3 mg. tuberculoprotein) intravenously which resulted in acute lethal anaphylactic shock within a few minutes.

Mother #3, also given an intravenous injection of filtrate containing 12.8 mg. tuberculoprotein, delivered twins two and one-half months after injection. Both young lived. Offspring A was given 1.5 cc. filtrate (0.8 mg. tuberculoprotein) intravenously when two months old and died immediately after injection in acute anaphylactic shock. Offspring B was given 2.5 cc. filtrate (1.35 mg. tuberculoprotein) intravenously at two and one-half months of age and died immediately in acute anaphylactic shock.

Mother #4, also given an intravenous injection of filtrate (20 cc. containing 12.8 mg. tuberculoprotein) delivered one offspring, eight months after the intravenous tuberculoprotein injection. This young guinea pig was given an intravenous injection of 5 cc.

filtrate (2.7 mg. tuberculoprotein) at one and one-half months after birth without revealing any anaphylactic reaction. Offspring B, born ten months after injecting the mother, was tested at two weeks of age by giving 1 cc. filtrate (0.54 mg. tuberculoprotein) intravenously and this offspring died immediately in acute anaphylactic shock.

It is evident from this experiment that tuberculoprotein anaphylactic hypersensitiveness can be passed from mother to offspring, born as long as ten months after the mother was given an intravenous injection of tuberculoprotein.

In view of the foregoing findings, further studies were initiated in which the mother guinea pigs were given an intraperitoneal injection of 3 cc. filtrate (1.6 mg. tuberculoprotein) and at intervals of about four days were given six subcutaneous injections of the same amount of the same filtrate.

Mother #1 gave birth to twins about three months after the first injection of filtrate. At the age of two months, offspring A was given an intravenous injection of 2 cc. filtrate (about 1 mg. tuberculoprotein) and died immediately in anaphylactic shock. At the age of six and one-half months, offspring B was given an intravenous injection of 5 cc. filtrate (2.7 mg. tuberculoprotein) and did not react.

Mother #2 gave birth to 3 young one year after the first injection of filtrate and 2 of these survived for tests. Offspring A was given an intravenous injection of 2 cc. filtrate (1 mg. tuberculoprotein) twenty days after birth and died immediately during acute anaphylactic shock. Offspring B was given 5 cc. filtrate (2.7 mg. tuberculoprotein) intravenously four and one-half months after birth and no reaction occurred. Following a rest period of three weeks, this guinea pig was again given an intravenous injection of filtrate, and 0.2 cc. (about 0.1 mg. tuberculoprotein) intravenously sufficed to produce an immediate acute lethal anaphylactic shock. At sixteen months, mother #2 gave birth to another young, offspring C, which was given an intravenous injection of 2 cc. filtrate (1 mg. tuberculoprotein) twenty-six days after birth, and this offspring died immediately with acute anaphylactic shock. About two years and four months after the initial intraperitoneal filtrate injection, mother #2 was given an intravenous injection of 5 cc. (2.7 mg. tuberculoprotein) filtrate and she died two and one-half hours after the injection without showing acute symptoms.

Mother #3 gave birth to offspring A five months after the initial injection of filtrate. At five weeks of age, this guinea pig was given an intravenous injection of 1 cc. filtrate (0.5 mg. tuberculoprotein) and it died immediately during anaphylactic shock. Two young, B and C, were born nine months after the initial filtrate injection. At the age of two months, offspring B was injected intravenously with 5 cc. filtrate (2.7 mg. tuberculoprotein) and died during anaphylactic shock. Offspring C was injected intravenously at the age of five months when 5 cc. filtrate (2.7 mg. tuberculoprotein) produced no reaction. Eleven months after the first filtrate injection, mother #3 gave birth to triplets, D, E and F. Offspring D was injected intravenously with 4 cc. filtrate (about 2.2 mg. tuberculoprotein) at the age of three months and died during acute anaphylactic shock. Offspring E was injected intravenously at three months of age but was given only 2 cc. filtrate (1.1 mg. tuberculoprotein) and, although reacting definitely anaphylactically, recovered. Offspring F was given 5 cc. filtrate (2.7 mg. tuberculoprotein) intravenously at four months of age and no appreciable reaction occurred. Mother #3 then gave birth to offspring G sixteen months after the first filtrate injection. At one month of age, an intravenous injection of 0.5 cc. (about 0.3 mg. tuberculoprotein) resulted in immediate anaphylactic death. Twenty-one months after her first filtrate injection, mother #3

gave birth to offspring H and I. At twenty-two days of age, offspring H was given intravenously 1 cc. filtrate (0.54 mg. tuberculoprotein) and died shortly during acute anaphylactic shock. Offspring I, at seven months of age, was given an intravenous injection of 5 cc. filtrate (2.7 mg. tuberculoprotein) but without any appreciable reaction. About three weeks after I's intravenous filtrate injection, 2 cc. filtrate intravenously proved acutely lethal anaphylactically. Finally, mother #3 was given an intravenous injection of 2 cc. filtrate (about 1 mg. tuberculoprotein) about two years after the initial intraperitoneal filtrate injection and died shortly during acute anaphylactic shock.

It is obvious from the foregoing experiments on guinea pigs that certain time and quantitative relationships exist between the tuberculoprotein sensitization of the recipient mother guinea pigs and the persistence of her anaphylactic hypersensitiveness to that of the *in utero* passage of this tuberculo-anaphylactic hypersensitiveness to her offspring. Although the hypersensitiveness wanes in the offspring with time after birth and may eventually disappear entirely, it is still passed from mother to offspring as long as twenty-one months after the initial tuberculoprotein injection was given to the mother. Tuberculoprotein anaphylactic hypersensitiveness can be definitely transferred from mother to offspring *in utero*, which is not the case with tuberculo-allergic hypersensitiveness as will be shown in the following experiments.

ATTEMPT TO PRODUCE TUBERCULO-ALLERGIC HYPERSENSITIVENESS BY MEANS OF HEAVY BACILLARY SUSPENSIONS

In the experiments planned to induce tuberculo-allergic hypersensitiveness, it was first tried by using avirulent human tubercle bacilli with the results recorded below. In these initial experiments, viable bacilli were obtained from cultures about two to four months old and the amount given subcutaneously to each female guinea pig was 20 mg. The bacilli were injected in fine suspension prepared in neutral saline solution (1 cc. containing 10 mg.). The injections were given subcutaneously in the lower left quadrant of the abdomen. Three mothers gave birth to young.

Mother #1 of this series gave birth to a young three months and three weeks after the injection of the avirulent tubercle bacilli. At the age of five weeks, this young guinea pig was given an intravenous injection of 0.1 cc. filtrate (0.05 mg. tuberculoprotein) intravenously and died shortly during typical anaphylactic shock.

Mother #2 gave birth to a sibling three months after the injection of avirulent human tubercle bacilli. At five weeks of age, this offspring was given 1.5 cc. filtrate (0.8 mg. tuberculoprotein) and died with typical anaphylactic shock in two minutes.

Mother #3 gave birth to 9 young at various times and 8 were tested. Offspring A and B, born three months after the injection of the avirulent tubercle bacilli into the mother, were tested at the age of four and one-half months. They received 5 cc. filtrate (2.7 mg. tuberculoprotein) intravenously and showed no reaction of any kind. Quadruplets were born to mother #3 ten months after the injection of the viable avirulent tubercle bacilli. Offspring C and D were tested at the age of one month by giving an intravenous injection of 1.5 cc. filtrate (0.8 mg. tuberculoprotein). Both died during typical acute anaphylactic shock. Offspring E and F were tested at the age of three months by giving an intravenous injection of 5 cc. filtrate (2.7 mg. tuberculoprotein) and no appreciable reaction occurred.

Offspring G and H were born one year after the mother was given the subcutaneous injection of the viable avirulent human tubercle bacilli. At the age of three weeks, offspring G received an intravenous injection of 0.5 cc. filtrate (about 0.3 mg. tuberculoprotein) and died during acute anaphylactic shock. At the age of five months, offspring H was tested by giving intravenously 5 cc. filtrate (2.7 mg. tuberculoprotein) and no appreciable reaction occurred. Three weeks after this injection, 2.8 cc. filtrate (1.5 mg. tuberculoprotein) intravenously caused acute anaphylactic shock and death. Mother #3 was then given an intravenous injection of 5 cc. filtrate (2.7 mg. tuberculoprotein) seventeen months after the injection of the 20 mg. of viable avirulent bacilli and a mild anaphylactic response was obtained from which she fully recovered in a short time. Three weeks later, she was again given 5 cc. filtrate (2.7 mg. tuberculoprotein) intravenously and only a slight acute response occurred with death following three days later.

The foregoing results would be confusing in that it might be assumed from the results obtained that tuberculo-anaphylactic hypersensitiveness and tuberculo-allergic hypersensitiveness were synonymous and could be induced by the bacillary suspension were it not for the fact that this was previously demonstrated not to be the case. Further, the two conditions could be produced in the same guinea pig (1), and both intoxications result from the appropriate final injection of tuberculoprotein into a tuberculous (allergic) animal which had previously received an injection of tuberculoprotein (the tuberculo-anaphylactogen) followed at an appropriate period of time by the final intoxicating dose of tuberculoprotein (filtrate). The foregoing experiments, therefore merit further elucidation in that the bacillary bodies obtained from older cultures of bacilli contained enough tuberculoprotein (adsorbed) which had been formed by the bacilli following prolonged culture and incubation to sensitize anaphylactically.

Although it is difficult to free bacilli from tuberculoprotein adsorbed during prolonged incubation, an attempt was made to do this in the following experiment by washing the bacilli by means of a number of changes of sterile saline. For convenience these are called washed bacilli. Two different amounts of washed avirulent human tubercle bacilli were used: one series of mothers was given 20 mg. intramuscularly in the hind leg (to avoid contamination of the young) and the other was given 1 mg. In the experiment in which 20 mg. of viable avirulent human tubercle bacilli were injected, 4 mothers gave birth to young.

Mother #1 had a sibling born five months after injection. At about one and one-half months of age, this young guinea pig was given an intravenous injection of 1.8 cc. filtrate (about 1 mg. tuberculoprotein) and died with acute anaphylactic shock. Another sibling was born fifteen months after the mother was injected. At the age of two weeks, this young was injected intravenously with 0.1 cc. filtrate and died with anaphylactic shock.

Mother #2 gave birth to triplets six months after the injection. At the ages of one, one, and two months one week, respectively, each died with anaphylactic shock after receiving intravenously 0.5 cc., 0.5 cc., and 0.2 cc. filtrate, respectively. Mother #2 gave birth to twins eleven months after injection. At about six weeks of age, both died with acute anaphylactic shock upon intravenous injection of 1 cc. filtrate (0.54 mg. tuberculoprotein).

Mother #3 delivered one live young eight and one-half months after the injection of the

washed bacilli. At the age of one month, this guinea pig received 0.1 cc. filtrate and died promptly with acute anaphylactic shock.

Mother #4 gave birth to a young four and one-half months after bacillary injection. At two weeks of age, this young received 3 cc. filtrate (1.6 mg. tuberculoprotein) without showing any appreciable response.

It is obvious that large amounts of bacilli carried tuberculoprotein which could not be removed by the washing used in these experiments. However, to further pursue this, another series of mothers was given only 1 mg. of washed bacilli with the following results.

Mother #1 gave birth to twins, A and B, seven months after the intramuscular bacillary injection of 1 mg. of washed viable avirulent human tubercle bacilli. At the age of one and one-half months, 5 cc. filtrate (2.7 mg. tuberculoprotein) elicited only a slight anaphylactic reaction. Another young, C, was born ten months after bacillary injection; and at the age of two months, 5 cc. filtrate (2.7 mg. tuberculoprotein) intravenously elicited no reaction.

Mother #2 gave birth to a young four months after intramuscular bacillary injection. At three weeks of age, an intravenous injection of 5 cc. filtrate (2.7 mg. tuberculoprotein) elicited no appreciable reaction.

Mother #3 was pregnant at time of bacillary injection and gave birth to a young twenty-three days later. When three months old, this young guinea pig received 5 cc. filtrate (2.7 mg. tuberculoprotein) intravenously without appreciable anaphylactic reaction.

It is evident here that although the viable avirulent tubercle bacilli can produce both allergic and anaphylactic tuberculoprotein hypersensitiveness (due to adsorbed tuberculoprotein) in the mother guinea pig when amounts as small as 1 mg. of bacilli derived from old cultures are injected, only the anaphylactic hypersensitiveness appears to be passed from mother to offspring with any regularity.

ABSENCE OF CONGENITAL TUBERCULO-ALLERGY

However, tuberculosis can be produced by extremely small infecting amounts of virulent human tubercle bacilli which completely obviate the introduction of tuberculoprotein as such and give way to the addition of bacillary bodies alone by multiplication. Consequent to this, tuberculosis and tuberculo-allergy result from the presence of these multiplying bacilli in the guinea pig economy. Thus, the infected and tuberculous mothers presenting tuberculo-allergy in classical manifestation should prove ideal for demonstrating the passage of tuberculo-allergy from mother to offspring. For this experiment, female guinea pigs were injected subcutaneously in the left side of the back, to avoid contamination of the young, with 0.000,000,1 mg. of a highly virulent human tubercle bacillus, H 160, and another series of mothers was given a slightly smaller amount, 0.000,000,01 mg. of bacilli. The findings among the mothers and young follow.

Series 1, mothers infected subcutaneously with 0.000,000,1 mg. virulent human tubercle bacilli (H 160):

Mother #1 gave birth to twins two months after infection. At the age of two months, both offspring, A and B, received an intravenous injection of 5 cc. filtrate (2.7 mg. tuberculoprotein) and no reaction occurred. This mother died five months after infection with a generalized tuberculosis of all the important internal organs.

Mother #2 gave birth to twins one and one-half months after infection. At the age of forty days, offspring A was given an intravenous injection of 5 cc. filtrate (2.7 mg. tuberculoprotein) without reaction of any kind. Offspring B, at the age of three and one-half months, was given an intravenous injection of 5 cc. filtrate (2.7 mg. tuberculoprotein) without reaction. This mother died five months after infection with a massive generalized tuberculosis.

Mother #3 had a young forty days after infection. At the age of one and one-half months, an intravenous injection of 5 cc. filtrate (2.7 mg. tuberculoprotein) failed to elicit any reaction. This mother died five months after infection with a generalized tuberculosis.

Series 2, mother guinea pigs infected subcutaneously with 0.000,000,01 mg. virulent human tubercle bacilli (H 160):

Mother #1 gave birth to a young seventy days after infection. At two and one-half months of age, this young guinea pig gave no reaction following the intravenous injection of 5 cc. filtrate (2.7 mg. tuberculoprotein). This mother died four months after infection and a generalized tuberculosis was found.

Mother #2 gave birth to a young two months after infection. At one month of age, no reaction followed the intravenous injection of 5 cc. filtrate (2.7 mg. tuberculoprotein). The mother died five months after infection with a generalized tuberculosis and polyserositis.

Mother #3 gave birth to twins three months after infection. At one month of age, offspring A was given an intravenous injection of 5 cc. filtrate (2.7 mg. tuberculoprotein) without reaction. At two months of age, offspring B also failed to react following the intravenous injection of 5 cc. filtrate (2.7 mg. tuberculoprotein). The mother died six months after infection and a generalized tuberculosis was found.

Numerous other offspring from tuberculous mothers were tested by giving an intravenous injection of filtrate, but there was no evidence to warrant the assumption that tuberculo-allergic hypersensitiveness is transmitted from tuberculous mother to offspring even though the mothers never failed to respond with the typical reaction of tuberculo-allergic intoxication either to a local injection of tuberculin or to an intravenous or subcutaneous injection in suitable dosage.

ABSENCE OF TUBERCULO-ALLERGIC IMMUNITY (DESENSITIZATION) IN OFFSPRING OF IMMUNE (DESENSITIZED) MOTHERS

Since it has been found that tuberculo-anaphylactic shock in guinea pigs can be produced consistently only by the intravenous injection of filtrate containing tuberculoprotein and tuberculo-allergic intoxication can be produced as

well when other routes of injection (subcutaneous, intraperitoneal, intracutaneous, etc., as well as intravenous) are used, it was possible to study another phase of this problem concerned with the passage of tuberculo-allergic immunity (desensitization) from mother to offspring. The mother was sensitized tuberculo-allergically by means of an injection of viable avirulent human tubercle bacilli (1 mg.) and then immunized (desensitized) against the tuberculo-allergy by giving spaced subcutaneous (to avoid anaphylactic shock) injections of filtrate (tuberculoprotein) for a long period of time. When the young were born, they were given an allergic sensitizing amount (1 mg.) of avirulent tubercle bacilli and, after an appropriate interval (about one month), they were tested by a subcutaneous injection (to avoid a tuberculo-anaphylactic response) of filtrate (tuberculoprotein). The results of this experiment were as follows:

The 20 mothers were given a subcutaneous injection 1 mg. of a three week old culture (low in tuberculoprotein). Two weeks after the bacillary injection, tuberculo-allergic immunization (desensitization) was begun by giving a subcutaneous injection of 1 cc. of a 1:4 dilution of natural filtrate (containing about 0.5 to 0.7 mg. tuberculoprotein per cc.) and injections were given at intervals of about six to ten days for a total of 33 injections. A few of the mothers died early from allergic intoxication consequent upon filtrate injection and a few from intercurrent infections, but 11 of them survived to give 27 offsprings suitable for test. All these 27 offspring were given a subcutaneous injection of 1 mg. viable avirulent human tubercle bacilli at varying intervals from two to four months after birth and one month later were given a subcutaneous injection of 5 cc. of filtrate (from 0.6 to 0.7 mg. tuberculoprotein per cc.). Of the 27 offspring, there were 9 young in the first series which were injected at the same time with six controls from normal mothers. The controls also received an injection of 1 mg. avirulent human tubercle bacilli. The results of the subcutaneous filtrate injection of 5 cc. were as follows: 7 of the test guinea pigs from allergic immunized mothers died within three hours, one died in thirty-six hours, and one died at seventy-two hours. The animals displayed typical allergic intoxication. Of the 6 controls, 4 died within 3 hours, and 2 died at seventy-two hours.

In the second series, there were 8 test young from allergic immunized (desensitized) mothers and 4 controls. Of the 8 test animals, 5 died within fifteen hours, 2 died within twenty-four hours, and one survived. Of the 4 controls, 3 died within fifteen hours and one died within twenty-four hours.

In the third series, there were 11 young from tuberculo-allergic immunized (desensitized) mothers and 4 controls from normal mothers. Of the 11 test guinea pigs, none survived overnight (about 14 hours). Of the control guinea pigs, 3 died overnight and one survived.

In summary, of the 27 test guinea pigs, 26 died during allergic intoxication within three days and only one survived; while of the 14 controls, 13 died within three days and 1 survived. It is apparent from these experiments that there is no definite evidence to indicate that specific tuberculo-allergic immunization (desensitization) by means of filtrate (tuberculoprotein) passes from mother guinea pig to offspring born during or following the injections given for the

purpose of specific allergic immunization (desensitization). Thus this resembles specific immunization against infection with virulent tubercle bacilli and specific tuberculo-allergic hypersensitiveness which must be produced by active contact with the tubercle bacilli and cannot be transmitted passively. On the other hand, specific tuberculoprotein anaphylactic hypersensitiveness differs from these in that it can be transferred passively with the blood as well as from mother to offspring guinea pigs.

SUMMARY

1. Tuberculo-anaphylactic hypersensitiveness in mother guinea pigs, produced by the injection of filtrates containing tuberculoprotein obtained from cultures of human tubercle bacilli on a nonprotein medium (Wong-Weinzirl), is regularly transferred to offspring born for over a year after sensitization of the mother. The tuberculo-anaphylactic hypersensitiveness may persist in the young in demonstrable form up to at least three months after birth.

2. Tuberculo-anaphylactic hypersensitiveness is not produced by tubercle bacilli or by tuberculosis; but when a sufficiently large amount of bacillary suspension of tubercle bacilli (20 mg.) or smaller amounts (1 mg.) of older cultures are injected, the amount of tuberculoprotein (or like products liberated by the bacilli during growth) is sufficient to sensitize anaphylactically. Washing with saline is not adequate to remove these products entirely when the bacilli are injected in large amounts.

3. Tuberculo-allergic hypersensitiveness in tuberculous mother guinea pigs, produced by small infecting amounts of virulent human tubercle bacilli, is not transferred to the offspring.

4. Tuberculo-allergic immunity (desensitization) in mother guinea pigs is not transferred to their offspring at any time during about a year while the mother is being desensitized or for six months thereafter.

5. These experiments further confirm the individuality of tuberculo-anaphylaxis and tuberculo-allergy as two separate biological reactions and suggest that biologically reactive tuberculoprotein as such is not present preformed in the tubercle bacillus nor does it appear to be liberated by these bacilli in the body.

SUMARIO

1. La hipersensibilidad tubérculo-anafilática de las cobayas hembras, producida por la inyección de filtrados que contienen tubérculoproteína obtenida de cultivos de bacilos tuberculosos humanos en un medio anaproteico (Wong-Weinzirl), es trasmitida con regularidad a la prole por más de un año después de desensibilizarse la madre. La hipersensibilidad tubérculo-anafiláctica puede persistir en los hijos en forma demostrable por lo menos hasta tres meses después del nacimiento.

2. La hipersensibilidad tubérculo-anafiláctica no es producida por bacilos tuberculosos o por tuberculosis, pero cuando se inyecta una cantidad suficiente de una suspensión bacilar de bacilos tuberculosos (20 mg.) o cantidades menores (1 mg.) de cultivos más viejos, la cantidad de tubérculoproteína (o de productos

semejantes emitidos por los bacilos durante su desarrollo), basta para desensibilizar anafilácticamente. El lavado con solución salina no basta para eliminar por completo esos productos cuando se inyectan grandes cantidades de bacilos.

3. La hipersensibilidad tubérculo-alérgica producida en las cobayas madres tuberculosas, por pequeñas cantidades infectantes de bacilos tuberculosos humanos, no es trasmitida a la prole.

4. La inmunidad tubérculo-alérgica (desensibilización) de las cobayas madres no es trasmitida tampoco a la prole aproximadamente por espacio de un año, mientras se desensibiliza la madre o por seis meses después.

5. Estos experimentos confirman, además, la individualidad de la tubérculo-anafilaxia y la tubérculo-alergia como reacciones biológicas independientes, e indica que la tubérculoproteína biológicamente reactora no está presente preformada en el bacilo tuberculoso, ni parece ser emitida por estos bacilos en el organismo.

REFERENCES

(1) Corper, H. J.: Analysis of the tubercle bacillus and its natural products by immune, allergic and anaphylactic tests, J. Infect. Dis., 1940, *66*, 23.

(2) Corper, H. J., and Cohn, Maurice L.: The effects of tuberculoprotein, A quantitative study, J. A. M. A., 1939, *112*, 403.

(3) Corper, H. J., Cohn, Maurice L., and Damerow, A. P.: Relations between specific immunity, allergy and anaphylaxis in tuberculosis, Am. J. Clin. Path., 1940, *10*, 361.

(4) Corper, H. J., and Cohn, Maurice L.: Intoxication in tuberculosis, Am. Rev. Tuberc., 1940, *41*, 71.

(5) Wong, Sam, and Weinzirl, John: An inexpensive synthetic medium for growing mycobacterium tuberculosis, Ibid., 1936, *33*, 577.

(6) Seibert, Florence B.: The chemical composition of the active principle of tuberculin, XI. An improved and simplified method for making a standard undenatured tuberculin of any desired strength and a method of chemical assay, J. Biol. Chem., 1928, *78*, 345.

INITIAL TISSUE RESPONSE TO TUBERCLE BACILLI[1, 2]

C. E. WOODRUFF, RUBY G. KELLY AND MARY A. LEAMING

The sequence of events which follows the parenteral introduction of tubercle bacilli has been studied extensively (1 to 8), and it is generally accepted at the present time that the bacilli are phagocytized first by polymorphonuclear leucocytes, then, after twelve to twenty-four hours, by large mononuclear cells which invade the area to ingest any remaining bacilli as well as the damaged granulocytes. This development of the inflammatory process was described in our own studies of the guinea pig omentum following the intraperitoneal inoculation of tubercle bacilli (9, 10). In addition it was discovered that during interval from the third to the seventh day after inoculation tubercle bacilli grow freely in, or on, the omental cells without attracting either polymorphonuclear or mononuclear phagocytes, while on the seventh day the bacilli which had been proliferating in perfect symbiosis with the omental cells again become subject to phagocytosis by polymorphonuclear leucocytes. The phagocytosis at this period we have explained as being due to the development of allergy in the experimental animal (10), but we were at a loss to explain the earlier sequence of events—why tubercle bacilli during the first few hours after inoculation should attract polymorphonuclear leucocytes while later, during the free growth period, they attract no phagocytes whatsoever.

Recently, in a series of animals inoculated intraperitoneally with various types of tubercle bacilli, omental spreads made three hours after inoculation showed, in every instance, small *clumps* of monocytes and polymorphonuclear cells on the surface of the omentum. Invariably these cell clumps were found to contain some of the inoculated tubercle bacilli. Thus we were prompted to reëxamine the cell reactions of the peritoneal cavity at earlier intervals after inoculation than had been employed in our previous studies. This search for the origin of the cell clumps on the omentum led to an answer to the question regarding the early inflammatory response to tubercle bacilli.

TECHNIQUE

The inoculum used in these experiments was made by carefully triturating a weighed amount of virulent, human type tubercle bacilli in a few drops of saline and then slowly adding saline until the suspension contained 0.2 mg. of tubercle bacilli per cc. Clumps of bacilli were present in the final suspension, no attempt being made to remove them.

Normal young guinea pigs, weighing from 200 to 300 g., were inoculated intraperitoneally through the right lower quadrant of the abdomen with 0.5 cc. of the tubercle bacillus suspension. The animals were sacrificed at intervals beginning five minutes after inoculation. At least two omental spreads were made from each animal, one being stained by Wright's method, the other by the Ziehl-Neelsen technique. Also, smears of the peri-

[1] From the Wm. H. Maybury Sanatorium (Detroit Municipal Tuberculosis Sanatorium), Northville, Michigan.

[2] Aided by a grant from the Committee on Medical Research of the National Tuberculosis Association.

toneal fluid were made and stained at the same time as the omental spreads. In some instances the Wright's stain preparation was examined and photographed, then was decolorized with acid-alcohol and restained using carbolfuchsin-methylene blue.

NATURE OF THE CELL CLUMPS

During the course of these experiments, 95 guinea pigs were sacrificed at intervals varying from five minutes to three hours after the intraperitoneal inoculation of 0.1 mg. of tubercle bacilli. In every instance cell clumps containing tubercle bacilli were found on the omentum. The clumps are seen in their most characteristic form fifteen to thirty minutes after inoculation. At this interval, they appear entirely adventitious as far as the omentum is concerned, looking as though they might have been dropped upon it (figures 1 and 2). Usually they bear no particular relation to the blood vessels, though occasionally they may come to rest against a capillary (figure 3).

In the preparations stained by Wright's method it can be seen that the cell clumps are made up chiefly of monocytes and eosinophils. Frequently, the esoinophilic cells in the clump are ruptured, and their granules are found scattered (figure 4). Preparations stained by the Ziehl-Neelsen technique show the monocytes more distinctly, but only the nuclei of the eosinophils can be seen. The Ziehl-Neelsen stain also brings into view the acid-fast bacilli which are invariably found in large numbers incorporated in the cell clumps (figures 5 and 6).

In an attempt to get an objective view of the composition of the clumps, differential cell counts have been made. Individual cell clumps in a Wright's stain preparation were marked, and the number of eosinophils determined. Then, after the same preparation had been decolorized and restained by the Ziehl-Neelsen method, the number of monocytes and lymphocytes in the clumps was determined. In all, 19 cell clumps, found in the omenta of 11 different animals, were studied in this way. In a total count of more than 900 cells the relative proportions of the various types of cells were found to be as follows: monocytes 89 per cent, eosinophils 9 per cent, lymphocytes 2 per cent.

A considerable variation was noted in the proportions of the cells found in different clumps, most of the smaller clumps being composed entirely of monocytes, while the larger clumps nearly always contained eosinophils in addition to the monocytes. The maximum proportion of eosinophils found in any one clump was 18 per cent.

FIG. 1. Cell clump on surface of omentum fifteen minutes after inoculation. × 110

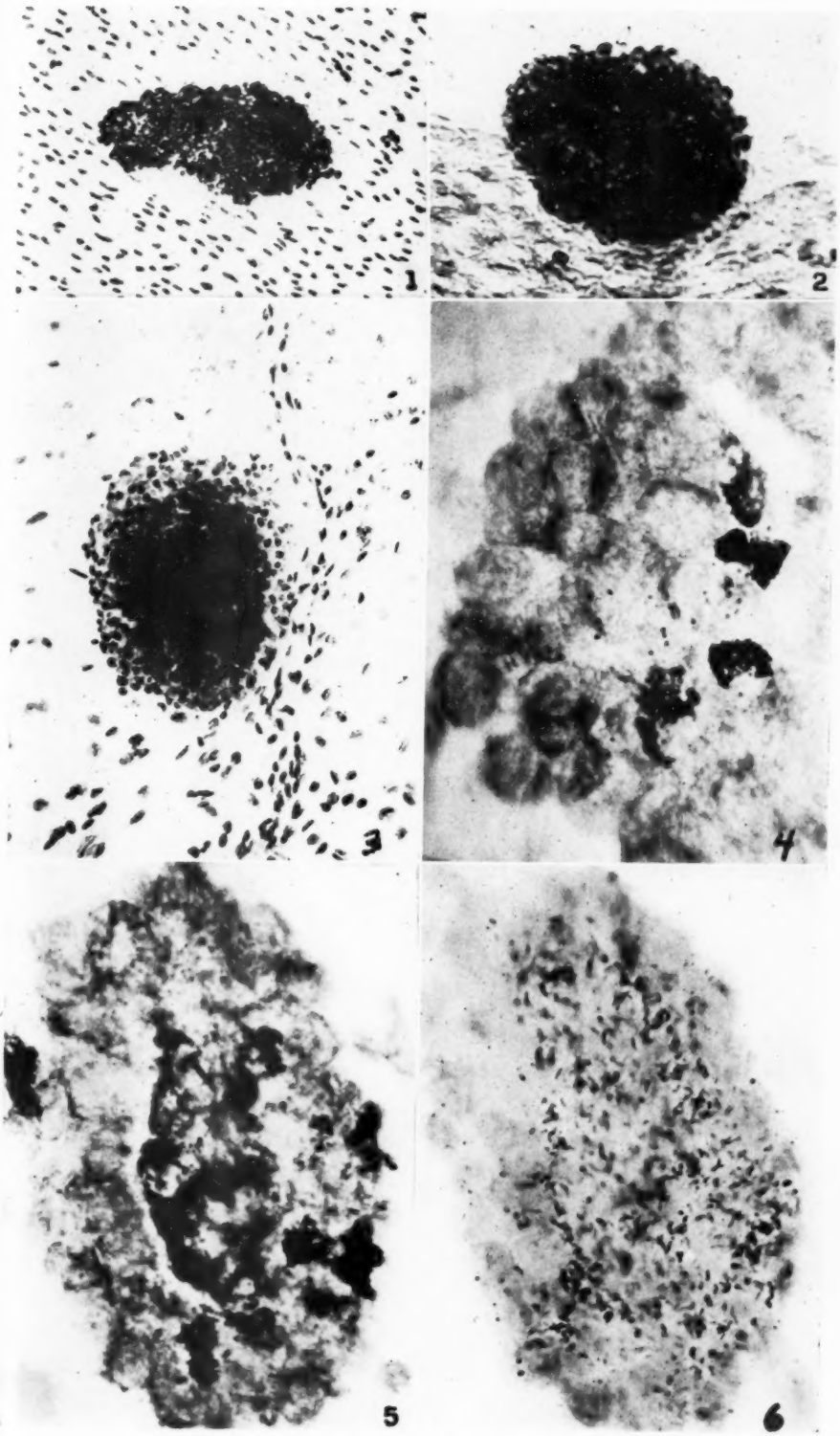
FIG. 2. Cell clump on omentum fifteen minutes after inoculation. The omentum is folded so that the clump stands out in bold relief. × 220

FIG. 3. Cell clump on omentum fifteen minutes after inoculation. The double line of cells just to the right of the clump is an omental capillary. × 170

FIG. 4. Portion of cell clump on the omentum. Wright's stain. The black masses are eosinophils and the black dots, eosinophilic granules.

FIG. 5. Cell clump on omentum fifteen minutes after inoculation. Wright's stain. The black masses are eosinophils. × 1100

FIG. 6. Same cell clump as shown in figure 5, decolorized and restained by Ziehl-Neelsen method to show tubercle bacilli. × 1100



FIGS. 1–6

RELATION BETWEEN PERITONEAL FLUID AND CELL CLUMPS

Gardner (11) has shown that the peritoneal fluid of the normal guinea pig contains, usually, about 74 per cent monocytes, 21 per cent eosinophils, 5 per cent lymphocytes and less than 0.2 per cent polymorphonuclear neutrophils, though in certain animals the lymphocytes were found increased to 40 per cent with a corresponding decrease in monocytes and eosinophils. Following the intraperitoneal inoculation of tubercle bacilli, Gardner found an abrupt decline in the proportion of monocytes in the peritoneal fluid and a temporary rise in the eosinophils. This was followed by a more sustained increase in the proportion of polymorphonuclear neutrophils. In order to follow these changes in our own animals differential counts of the cells of the peritoneal fluid have been made and omental spreads from the same animals have been studied. From a comparison of the changes occurring simultaneously in the peritoneal fluid

TABLE 1

Early changes which follow the inoculation of 0.1 mg. of tubercle bacilli into the peritoneal cavity of normal guinea pigs

ANIMAL NUMBER	INTERVAL AFTER INOCULATION	DIFFERENTIAL COUNT IN PER CENT OF CELLS IN PERITONEAL FLUID				NUMBER OF CELLS IN FLUID	SIZE OF CELL CLUMPS ON OMENTUM	SIGNS OF INFLAMMATION
		Monocytes	Eosinophils	Lymphocytes	Neutrophils			
4386	5 min.	71	27	2	0	Numerous	Very small	0
4387	15 min.	43	55	2	0	Numerous	Large	0
4388	30 min.	26	70	4	0	Few	Large	0
4389	1 hr.	19	67	11	3	Few	Very large	Slight
4390	2 hr.	7	12	8	73	Numerous	Very large	Marked
4391	3 hr.	3	4	2	91	Very numerous	Very large	Marked

NOTE: As indicated, the figures given in table 1 represent, at each time interval, the cell percentage in the peritoneal fluid of a single animal. In our other experimental series the cell counts, though showing individual variations, have constantly indicated the same *trend* in the cell counts with the lapse of time.

and in the omentum of a given animal one obtains a complete picture of the events which follow the intraperitoneal inoculation of tubercle bacilli. In table 1 the results of such an experiment are given.

In figures 7 to 14 will be seen photomicrographs of the preparations which were used in compiling table 1. Figure 7, showing a stained smear of the peritoneal fluid five minutes after inoculation, gives an idea of the relative proportions of monocytes and eosinophils. It will be noted that the monocytes are beginning to clump together and that only occasional eosinophils are included in the clumps. In figure 8, showing peritoneal fluid from the same animal stained by Ziehl-Neelsen's method, it will be seen that many of the monocytes have already taken up tubercle bacilli while none of the eosinophils have, as yet, phagocytized bacilli. A count was made to determine the proportion of cells which, at the five-minute interval, had phagocytized tubercle bacilli. In

table 2 may be seen the combined results obtained from making such counts on the peritoneal fluid of 6 animals sacrificed at the five-minute interval.

Figure 9 shows part of an omental preparation made five minutes after inoculation. It will be noted that already some of the cell clumps have reached, and adhered to, the omentum. At this early interval, the clumps are quite small and are usually made up entirely of monocytes.

Fifteen minutes after inoculation much larger cell clumps are found on the omentum (figure 10). These clumps, while containing both monocytes and eosinophils, usually have about ten times as many of the former type of cells as the latter. As indicated in table 1, the peritoneal fluid at the fifteen-minute interval, with its decreased proportion of monocytes, begins to show the effect of the removal of this type of cell.

Thirty minutes following inoculation even larger clumps are found on the omentum (figure 11), and the remaining cells in the peritoneal fluid are largely eosinophils (figure 12). Dworski, Smith and Gardner (12) found that thirty minutes after infection nearly 50 per cent of the eosinophils in the peritoneal fluid contain tubercle bacilli. We, too, have observed at this interval that a considerably increased proportion of the eosinophils contains tubercle bacilli.

TABLE 2

Phagocytosis of tubercle bacilli by cells of the peritoneal fluid five minutes after inoculation

TYPE OF CELLS	NUMBER OF CELLS COUNTED	PROPORTION OF CELLS CONTAINING TUBERCLE BACILLI
Monocytes	637	46%
Eosinophils	340	3%

Undoubtedly this is due to the fact that most of the phagocytic monocytes already have become agglutinated and thus have been removed from the peritoneal fluid.

At the one-hour interval the first signs of a true inflammatory reaction are noted in the slight injection of the omental capillaries and the beginning appearance of polymorphonuclear neutrophils in the peritoneal fluid. Two hours after inoculation the omentum appears markedly inflamed, and the peritoneal fluid again contains numerous cells, most of them being neutrophils. At three hours the peritoneal fluid is highly cellular containing, as indicated in table 1, more than 90 per cent polymorphonuclear neutrophils. Figure 13 gives the appearance of the peritoneal fluid at this time while figure 14 shows how the cell clumps on the omentum have now become completely surrounded by polymorphonuclear leucocytes.

CONTROL PREPARATIONS

It has been pointed out by Gardner (3) that the early cell changes which follow the intraperitoneal inoculation of tubercle bacilli are nonspecific in character. Our own observations are corroborative. After the intraperitoneal in-

oculation of 0.1 mg. of staphylococci suspended in 0.5 cc. of saline, cell clumps made up of monocytes and eosinophils and containing staphylococci are found in the omentum, this initial reaction being followed after about one hour by the inflammatory response. The same sequence of events follows the inoculation of a suspension of lamp black or of india ink. Apparently the monocytes phagocytize any particulate material which may reach the peritoneal cavity. They then become agglutinated, and the constant current of lymph brings the groups of agglutinated cells into contact with the omentum. Not until about an hour has elapsed does the true inflammatory response appear.

The cell clumps are not found on the omenta of uninoculated, healthy guinea pigs. However, in 2 instances we have found them on the omenta of stock animals which were sacrificed because they appeared sickly, and in both of these instances the cell clumps contained bacteria.

ALLERGIC ANIMALS

Omental preparations from a few guinea pigs which were already allergic at the time of their intraperitoneal inoculation have been studied. The initial reaction in these animals is phagocytosis of the tubercle bacilli by monocytes followed by agglutination of the cells and a delayed inflammatory response just as occurs in the normal guinea pig. Apparently, as Gardner (3) has said, "Reinfection in the peritoneal cavity of animals previously sensitized by subcutaneous inoculations is met by the same type of cellular reactions as those found in primary infections of normal guinea pigs." We have not experimented with enough of the allergic animals to be able to say whether the inflammatory response in the peritoneal cavity occurs more quickly in allergic than in normal guinea pigs.

FIG. 7. Peritoneal fluid five minutes after inoculation. Wright's stain. The monocytes are clumped together. Two eosinophils are included in the clump. × 980

FIG. 8. Peritoneal fluid five minutes after inoculation. Ziehl-Neelsen stain. Many tubercle bacilli have been phagocytized by the monocytes but none, as yet, by the eosinophils. × 980

FIG. 9. Omentum five minutes after inoculation showing a clump of cells with tubercle bacilli. Ziehl-Neelsen stain. × 980

FIG. 10. Cell clump on surface of omentum fifteen minutes after inoculation. Wright's stain. The black dots are eosinophils. × 110

FIG. 11. Cell clump on omentum thirty minutes after inoculation. Wright's stain. The fragile character of the clump is indicated by the line of fracture which was caused by the pressure of the coverslip. × 110

FIG. 12. Peritoneal fluid thirty minutes after inoculation, illustrating the paucity of cells. There are 4 eosinophils, the cell in the lower left corner being the only monocyte. Wright's stain. × 980

FIG. 13. Peritoneal fluid three hours after inoculation. Most of the cells are polymorphonuclear neutrophils. × 980

FIG. 14. Omentum two hours after inoculation. Cell clump is surrounded by leucocytes. On the left side of the picture the elastic fibres of the omental net show clearly. × 110

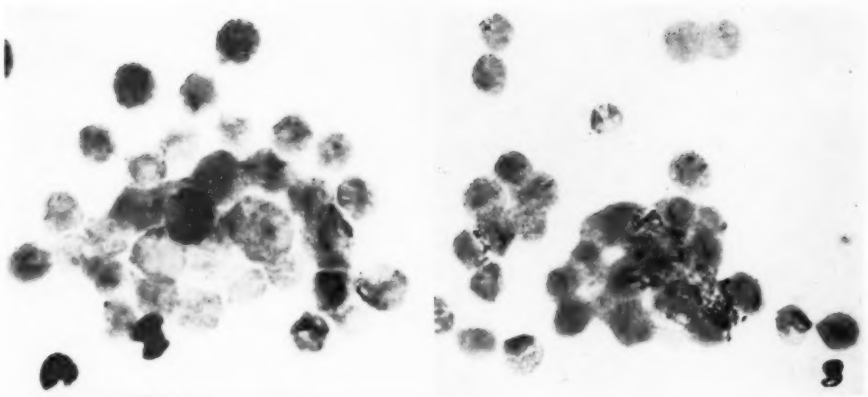


FIG. 7

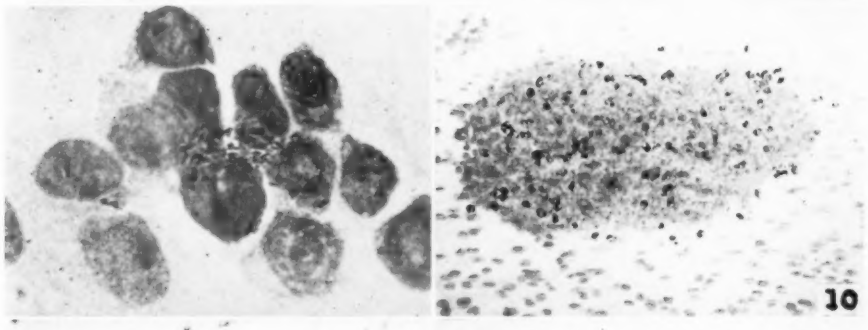
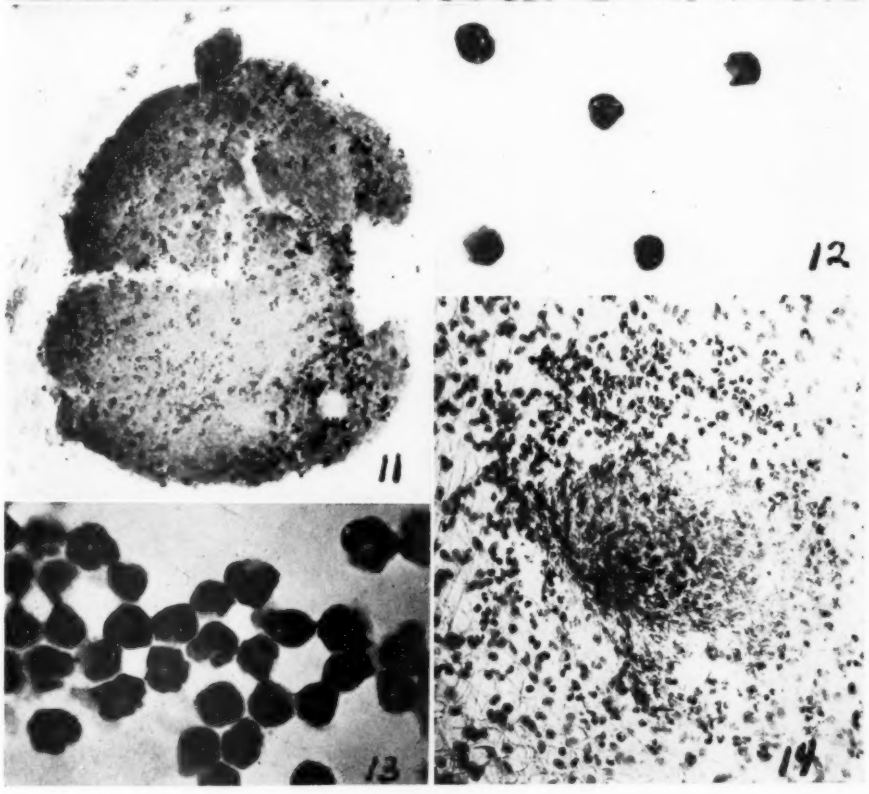


FIG. 9



FIGS. 7–14

DISCUSSION

When bacteria or other minute particles gain access to the peritoneal cavity of the guinea pig, the ever present policemen (monocytes) go into action against the invader and become agglutinated before true inflammation occurs. Remembering the fact that cell injury is the only adequate stimulus for inflammation, the sequence of events seems clear. Menkin (13) has isolated the substance *leucotaxine* which is liberated by injured cells. This substance causes a marked increase in capillary permeability in the area of its application and affects the migration of leucocytes. Borquist and Rowe (14) have shown that monocytes are much more fragile and easily disintegrated than are clasmatocytes. Thus, it would seem that the injury to the monocytes in the peritoneal fluid, during and after their agglutination, is in the nature of a trigger action which fires the inflammatory gun and results, eventually, in the overwhelming outpouring of polymorphonuclear neutrophils. Or, to use another metaphor, the cries of a few injured policemen bring a whole army of neutrophils running to the scene of action.

Obviously the demonstration that the monocyte is the primary phagocytic cell of the peritoneal fluid does not negate those studies which have been made using a different locus of experimentation. Thus, after the intravenous inoculation of tubercle bacilli one might expect that when the bacilli localize within pulmonary capillaries polymorphonuclear leucocytes would be the first cells to phagocytize the infectious agent, as has been reported (1, 6, 8). However, in what might be considered a more natural mode of infecting the lung—the introduction of tubercle bacilli through the air passages—conditions simulate more closely those which obtain in the peritoneal cavity. In both cases we are dealing with a sac lined by flat pavement cells of mesodermal origin (15). In both locations the phagocytic cell normally present is one of the macrophage group (16). Furthermore, the work of Jensen, Bindslev and Holm (17) on guinea pigs infected by the inspiration of tubercle bacilli indicates that the bacilli may gain access to the alveolar lining cells and experience a free growth period there, just as occurs when the bacilli become localized in cells of the omentum.

From the foregoing discussion a possible explanation of the free growth period of tubercle bacilli becomes evident. When inoculated intraperitoneally the bacilli, first phagocytized by monocytes, call forth polymorphonuclear neutrophils as the result of a nonspecific reaction peculiar to the serous cavity. Those bacilli which adhere to the omental cells are protected from this initial phagocytosis and proliferate without hindrance as long as they cause no injury to the host cell. Thus, the free growth period of the bacilli occurs. Then about the seventh day, as the tissues become allergic, the tubercle bacilli *do* injure their host cells and again call forth polymorphonuclear phagocytes.

SUMMARY

1. Tubercle bacilli inoculated intraperitoneally in guinea pigs are phagocytized within a few minutes by the monocytes which occur normally in the peritoneal fluid; to a lesser extent by the eosinophils.

2. These phagocytic cells rapidly become agglutinated and the clumps of agglutinated cells adhere to the omentum.

3. The true inflammatory response, beginning after about an hour, is probably initiated by the injury to the agglutinated monocytes. Thus, after the intraperitoneal inoculation of tubercle bacilli in the guinea pig, *phagocytosis* and *agglutination* precede *inflammation*.

4. A comparison is drawn between the inflammatory process as it occurs in the peritoneal cavity and in the pulmonary alveoli.

SUMARIO

1. Los bacilos tuberculosos inoculados intraperitonealmente en los cobayos son fagocitados a los pocos minutos por los monocitos que se presentan normalmente en el líquido peritoneal, y en menor grado por los eosinófilos.

2. Las células fagocitarias rápidamente se aglutinan y los grupos de células aglutinantes se adhieren al epiplón.

3. La verdadera respuesta inflamatoria que comienza, aproximadamente a la hora, es probablemente iniciada por la lesión de los monocitos aglutinados; es decir, que después una inoculación intraperitoneal de bacilos tuberculosos en el cobayo, la *fagocitosis* y la *aglutinación* preceden a la *inflamación*.

4. Trázase una comparación entre el proceso inflamatorio tal como se presenta en la cavidad peritoneal y en los alvéolos pulmonares.

The authors wish to express their appreciation for the suggestions made and advice given by Dr. H. S. Willis during the course of these experiments.

BIBLIOGRAPHY

(1) Borrel, A.: Tuberculose pulmonaire expérimentale, Ann. Inst. Pasteur, 1893, *7*, 593.

(2) Gardner, L. U.: Studies on the tissue reactions to primary infection and reinfection with the tubercle bacillus, I. A histological examination of the omentum and other subperitoneal tissues, Am. Rev. Tuberc., 1929, *20*, 201.

(3) Gardner, L. U.: The cellular reactions to primary infection and reinfection with the tubercle bacillus, II. The cells of the peritoneal exudate produced by the local injection of tubercle bacilli into normal and sensitized guinea pigs, Ibid., 1930, *22*, 379.

(4) Long, E. R., Vorwald, A. J., and Donaldson, L.: Early cellular reaction to tubercle bacilli, Arch. Path., 1931, *12*, 956.

(5) Albert-Weil, J.: Les réactions cellulaires dans la tuberculose, Ann. de méd., 1931, *30*, 444.

(6) Vorwald, A. J.: The early cellular reactions in the lungs of rabbits injected intravenously with tubercle bacilli, Am. Rev. Tuberc., 1932, *25*, 74.

(7) Long, E. R., Holley, S. W., and Vorwald, A. J.: A comparison of the cellular reaction in experimental tuberculosis of the cornea in animals of varying resistance, Am. J. Path., 1933, *9*, 329.

(8) Rosenthal, S. R.: Focal and general tissue responses to an avirulent tubercle bacillus (BCG), Arch. Path., 1936, *22*, 348.

(9) Woodruff, C. E.: A free growth period of tubercle bacilli in the guinea pig omentum as related to the hypersensitive state, Am. J. Path., 1934, *10*, 739.

(10) Woodruff, C. E., and Kelly, Ruby, G.: Growth of tubercle bacilli in tissues of normal and allergic guinea pigs, Am. Rev. Tuberc., 1940, *42*, 782.

(11) Gardner, L. U.: Differential cell count of peritoneal fluid from normal guinea pig, Proc. Soc. Exper. Biol. & Med., 1929, *26*, 690.

(12) Dworski, M., Smith, D. T., and Gardner, L. U.: A comparative study of the cytological reactions to primary and superinfection with the tubercle bacillus in the guinea pig, Tr. Nat. Tubere. A., 1925, p. 321.

(13) Menkin, V.: The rôle of inflammation in immunity, Physiol. Rev., 1938, *18*, 366.

(14) Borquist, May, and Rowe, C.: The phagocytosis of tubercle bacilli by leucocytes, Am. Rev. Tubere., 1931, *24*, 172.

(15) Gay, F. P.: Tissue resistance and immunity, J. A. M. A., 1931, *97*, 1193.

(16) Sabin, Florence R., and Doan, C. A.: The relation of monocytes and clasmatocytes to early infection in rabbits with bovine tubercle bacilli, J. Exper. Med., 1927, *46*, 627.

(17) Jensen, K. A., Bindslev, G., and Holm, J.: Experimental studies on the development of tuberculous infection in allergic and non-allergic animals, Acta tubere. Scandinav., 1937, *9*, 27.

AGE CHARACTERISTICS OF TUBERCLES[1]

HENRY C. SWEANY

In a recent work I (1) reported certain changes that take place during the aging of primary tubercles. In the principal series of cases the changes observed were correlated with elapsed time, by studying patients on whom there was a definite history of contact, followed by a rather prompt breaking of contact. After death of the infected patient the primary tubercles were arranged according to their ages and the character of the tubercles at each age period were studied and charted. It was observed that there were many alterations in morphology as the tubercles became older, some of which seemed to be constant for rather definite age periods. The changes observed were meticulously described and the important ones seemed to be sufficiently constant to warrant their use, not only for approximating the ages of the tubercles, but also for a potential guide in tracing the course of the disease in the body.

As may be expected in a new work of this nature, there will be obscure features in need of clarification. Some of the important and controversial points are: first, the accuracy with which the duration of the primary infections could be determined; second, adequate exclusion of later infections; third, the size of the series of cases studied; and fourth, the variations occurring in lesions and the extent to which they interfere with the system of age-determination of tubercles. The first two objections were ruled out largely by a rigid selection of cases so that only rare "casual" reinfections were possible. As to the third objection, it must be admitted that the size of the main series is smaller than desirable. There were only 27 cases where the history was sufficiently accurate to use, and 3 (11.1 per cent) of these offered no suitable data for study. Most of the other cases referred to later in the book, however, had accurate histories of contact; but the contacts occurred after seven years of age, so that an earlier infection could not definitely be precluded, even if earlier infections were not found. In a small percentage of the second group, no doubt, later infections occurred than the ones suspected from the history, but in over 85 per cent there was the same general pattern of change that was found in the first series. It was felt that this series coincided so well with the first and that more than 85 per cent agreement of cases was so great that it was entirely beyond any consideration of coincidence. On the whole, there was a certain character for each age period beyond which no lesion with accurate history was ever found to deviate. The last objection is perhaps the most difficult to answer and will be given the most attention in this report.

As pointed out in the book, the conception of the age-morphology relationship is essentially new. The work of Ghon (2), Blacklock (3), Lange (4), however, and especially Huebschmann (5), suggests the possibility; and Jaffé and Levinson (6), Schürmann (7), Puder (8) and others, without attempting to establish

[1] From the Research Laboratories of the City of Chicago Municipal Tuberculosis Sanitarium, Chicago, Illinois.

any relationship of age to morphology, actually show that the presence of bone, to mention only one factor, increases in the older age group of patients.

Grethmann (9), on the other hand, dogmatically denied that any such relationship exists, and apparently Terplan (10)[2] and perhaps others have similar views. It is clear that such divergent opinions are due to entirely different experiences with and interpretations of pathological material. It is the purpose of this exposition to reconcile some of the opposing views, or at least to present the facts from my point of view as I have interpreted them. Time will then appraise the results in proportion as it does or does not serve a useful purpose.

In the report to follow, therefore, a brief review of the age-morphology principle will be presented, to be followed by a discussion of the apparent exceptions and controversial points, as well as the means used in recognizing and discounting them. Convenient illustrations are used for certain unusual types not ordinarily encountered.

Formerly calcified tubercles were referred to as "tombstones" (11) of an old tuberculous focus. It is to be hoped that in the future it may be possible to utilize some of them as a "blazed trail" for following the course of the disease in the body. In this endeavor it has been found expedient to study the phenomena under several broad divisions in a chronological sequence, namely, acute inflammatory reaction; degeneration of cells of the focus; encapsulation and sterilization of the debris; disintegration and resorption of the sterile mass. All will agree that tubercles go through these stages in their evolution roughly in the order given, even if there is not agreement on the time it takes to do it.

At this late date there should be no greatly divided opinions on the early changes within a tubercle. Notwithstanding the scarcity of human material, extensive animal experimentation has afforded a clear conception of the general

[2] Terplan (10), in a recent review, took exceptions to the principles and much of the details of the work. While much of the criticism may be charged off as a reviewer's rightful opinion, there are some errors that demand correction. For example, he labored under a grave misapprehension when he objected to "900 cases" which he assumed were used, stating that "progress in our knowledge of tuberculosis in man is better served by more thorough analysis of a smaller material." The facts are that only 166 cases were tabulated and 103 described out of a whole series of 900 postmortem examinations. Another careless quotation was in citing 30 for 27 cases in the first series and 11 for 12 as the size limit of tubercles. "Tubercles in the diameter of the cerebellum" should have been reported as a typographical error. "Piamater" for "diameter" gives it meaning. There was also a blanket criticism regarding the way cases were presented, when in the preface the highly specialized nature of the work was clearly pointed out. "All factors pertaining to the main thesis—the relationship of age to morphology of primary tubercles—have been given in minute detail with almost tedious routine, and other important data not related to this idea have been omitted." In view of the cost of paper, not to mention the reader's time, this seems like a reasonable position. I expressed regret regarding "arithmetic terms" as follows: "Although crude and having an appearance of *false accuracy* (italics new), the numerical method is the best way to remove the personal element. *The limits of error are, therefore, 25 per cent either way.*" The criticism of new terms is more a personal opinion and will apply to every writer since Hippocrates. New, simple and expressive terms are the means of enrichment of a language. That is how the expressive terms "caseous," "calcified," "petrified" and a hundred more came into use.

reaction in spite of the risk in applying animal to human problems. It is axiomatic that the first few weeks represent acute inflammation which gradually veers over into subacute and then chronic changes. It is an aveolitis, a bronchopneumonic or pneumonic focus (depending on the total area involved) that in the retrogressive types becomes stabilized after two to three months and then gradually undergoes encapsulation by fibrous tissue. There are no doubt variations from one to another, but in *moderately sized retrogressive lesions* the changes have been found to be remarkably constant. The first nebulous mass becomes circumscribed, the centre caseates, monocytes accumulate in varying numbers around the periphery and become transformed into fibroblasts. No doubt fibroblasts also originate from the reticulum *in situ*. Varying degrees of caseation develop that either spread more rapidly than the capsule can form in progressive lesions or slow enough for the lesion to reach equilibrium and encapsulation in the retrogressive types.

The caseation is not necessarily a uniform procedure. There are differences of degree from one lesion to another and even within different areas of the same lesion.

Caseation undoubtedly destroys parenchymal and, in fact, most of the highly specialized cells, but many of the connective tissue elements remain intact for long intervals. Not infrequently large areas of calcification may become resorbed and the remaining connective and reticulum tissue will begin to proliferate, forming fibroid tissue in which capillaries and sometimes bone cells develop. Tuberculous foci generally are irregular in their disintegration. Special stains reveal that most tubercles will have areas of destruction of all tissues; other areas will show only elastic and reticulum tissue; while other areas may show collagenous fibres and other cell remnants.

As it is not always easy to find rapidly progressive early lesions, a case will be reported to demonstrate an age-morphology relationship in lesions of no more than three to four months' duration.

Case 1: A1470 was a nineteen year old girl of Italian descent. Very little history could be elicited from the patient because she was practically moribund. The patient died two days after admission. The onset was with sore throat and cough six weeks before death.

There were râles from the apex to the base in both lungs. The laboratory findings were negative. The diagnosis was pulmonary tuberculosis, F. A. B., questionably miliary.

The postmortem examination revealed a focal fibrous adhesion in the left subapical region under which was a cluster of caseous foci, the oldest part of which was about 5 mm. in diameter. There was much involvement around this focus and corresponding lymph node tubercles in the bronchopulmonary nodes and the nodes at the hilum. A generalized miliary tuberculosis involved practically every organ and tissue. Many lesions in the lungs had spread beyond the miliary stage and assumed typical acinous characteristics. The capsule of the pulmonary foci had no evidence of a monocytic layer at all. There were several fibers of lung stroma outside the caseous centre. The tubercles corresponded to those seen elsewhere of only three to four months of age. An important feature was the utter lack of host "resistance" in spite of the presence of giant cells. Acid-fast bacilli, on direct section stain, were found only in the spleen and then only in small numbers. (Plate I.)

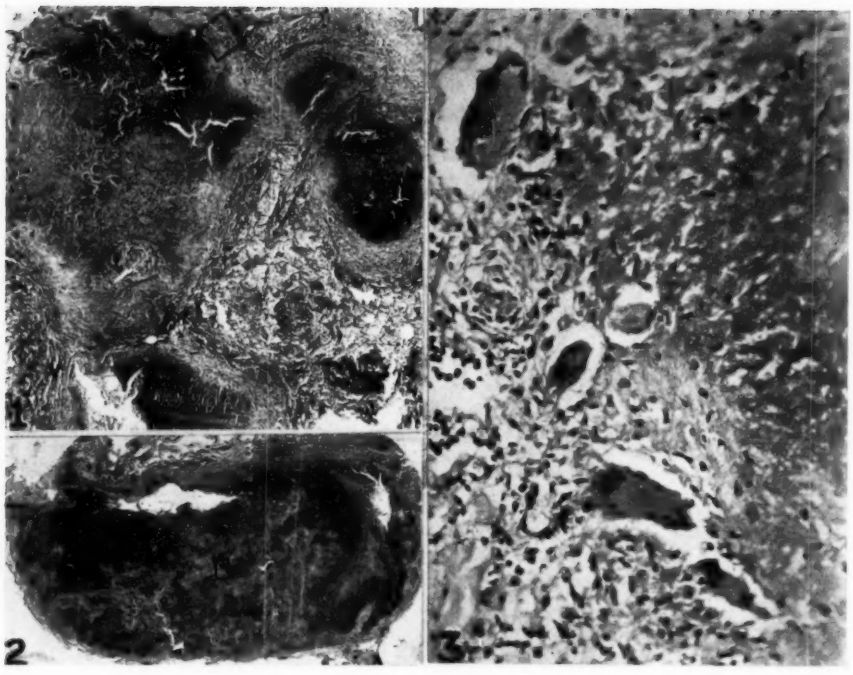


PLATE I

FIG. 1. Parenchymal primary lesion in case 1, A1470, A. B., showing an early caseous centre with a thin nonspecific capsule of stroma but no signs of specific capsule. H & E × 11

FIG. 2. A section of one of the many lymph node lesions near the hilum. Diffuse early caseation exists throughout. H & E × 4

FIG. 3. Shows a segment of the capsule outlined in the square of figure 2. Note the nonspecific character of the fibres and the giant cells extending out to the periphery. No acid-fast bacilli were found on these sections. H & E × 183

Between four and eight months a definite capsule forms, which at first is composed only of a few fibres, principally of alveolar tissue stroma. Gradually a monocytic layer forms from "epithelioid cells" and reaches its maximum at about three years. This layer has been designated the "inner" capsule by Pagel (12) and the "specific" capsule by Aschoff (13). It fuses with heavy fibrous tissue into a heavy "middle" capsule up to seven or eight years. The designation "middle capsule" is new, because it represents heavy hyalinized nonspecific fibres of a later era than the true inner capsule. At about the five-year period there begins the first sign of disintegration of the tubercle. The calcification which begins after a few months' time in the centre of the tubercle extends as microscopical foci until the whole core is involved. The process seems to develop in small globules of autolyzed debris consisting of fatty acids or other acid radicals which combine with the calcium ions to form the solid soaps and calcium salts.

This process, however, is by no means all that occurs or even the most important change. In the layer of fibrous tissue of the capsule next to the calcified core, there is an apparent reawakening of activity of some of the cells at different points around the circumference. Whether the reactivated cells are revitalized fibrocytes (as they sometimes appear to be), or incarcerated mesenchymal cells, or reactivated reticulum, is as yet unknown. Furthermore, the problem does not lend itself to ready solution, as no artificial tubercle can be prepared and studied after so long a time. All that is possible, therefore, is to describe the phenomenon in a large series of tubercles and draw deductions regarding the origin of the cells and tissues.

It has been noted and described in several places (14) that the cells vary greatly in shape, size and character, but it may be that the changes are only different stages of revival of the same cell type. At first the cells have thin nuclei which enlarge and finally appear much like young fibroblasts. It is possible that there is a reversal of fibrocytes to fibroblasts much the same as the reversal of osteocytes to osteoblasts in the absence of ascorbic acid.

The first evidences of activity are clefts in between the capsule and core appearing like artefacts. On close inspection the clefts take on a moth-eaten appearance around the edges, or perhaps it is best compared to the erosions in cheese caused by the teeth of mice. Along the margins of unexcavated parts may be seen the cells that have been formerly described (6, 13). They appear to grow into the calcification on the core side and into the collagen of the capsule. Inasmuch as this phenomenon is relatively new, it is perhaps desirable to give another illustration than the one given in the book. If serial sections are made, every case of true resorption may be found to reveal one of the various types of cells mentioned in close association with the erosions and may be properly suspected of a connection with them.

An illustration will be given:

Case 2: A1330 was a 27.4 year old American of Jugoslav descent. His mother died of tuberculosis when he was seven months old. His father-in-law died of tuberculosis two

years before the patient's death. The onset of his disease was with cough nine months before death. A diagnosis was made in April, 1940 when he took his child to a clinic for persistent "eczema." A tuberculin test was found positive and an infiltrate was discovered on an X-ray film of the child's chest, whereupon the father (this patient) was advised to have a chest X-ray examination, which revealed tuberculosis. The clinical course was rapidly downward from admission in June until death in August, 1940. Many of the common symptoms began in March, 1940, including fever, night sweats, dyspnoea, hoarseness, pain in throat, for which a superior laryngeal nerve resection was performed in June.

At autopsy there was found an abortive (adult) type of primary tuberculosis in the right upper lobe, consisting of about ten calcified lesions 3 to 5 mm. in diameter of approximately ten years' duration. There were two or three 2 to 3 mm. corresponding lesions in the lymph nodes. There was a scattered fibrocaseous and fibroid tuberculosis throughout the same lobe and also a generalized miliary tuberculosis throughout the body. The source of the generalized process was not found in the lungs despite a complete slicing of the organ in slices 2 mm. in thickness. The character of the miliary lesions, however, was worthy of note in that they had a tendency to be fibrotic in the posterior and subapical regions of both lungs and gradually enlarged with increasing exudation and numbers of bacilli in the anterior and caudal parts. There could be seen a gradual transition from one type to the other. In the extreme anterior parts there were overflowing lesions that spread in an acinous-nodose fashion into adjacent alveoli. Some were actually undergoing ulceration into small cavities and opening into bronchioles. (Plate II.)

Comment: The principal feature of the illustrations is to show the resorption going on in the tubercle. The cells illustrated are fairly representative of the process, from the small ones in figure 2 to the larger, fibroblast-like cells, in figure 3. In other reports (15) it has been shown that the latter cell resembles the ones that become transformed into bone.

At about the eight-year period the lacunae may become large and extend half way or more through the capsule up to twelve and fifteen years so that capillaries from without many times penetrate the lacunae and form a network within (16). At one time it was thought that this capillary invasion was probably related to bone formation, but now I am not so certain. Bone is perhaps due more to a balance of certain ions (Ca, P, etc.) and their concentration within the particular area rather than a result of capillary penetration. Although practically all bony lesions reveal capillaries, there is little doubt that bone formation may begin and extend without capillary penetration. It seems to be more certain, however, that the capillaries must be present for the formation of marrow elements as no marrow has ever been found without them.

As the resorption and cellular proliferation continues (as well as capillary penetration) there comes a time when the cells that have been described before become angular and appear to take on a deep stain resembling bone. The earliest bone in this series was ten years, but it is not improbable that bone may appear earlier under certain favorable circumstances including very small lesions. The majority of tubercles show well developed bone by fifteen years and practically all by twenty years.

There are other changes in the tubercle which are not strictly or only roughly

PLATE II

FIG. 1. A small lymph node calcified tubercle of a ten-year age rating (somewhere between 8.0 to 12.5 years) showing large clefts of resorption and the areas enlarged in figures 2 and 3. H & E × 76

FIG. 2. Lower enlarged area from figure 1, showing cells having a dense nucleus and an even cytoplasm "budding" off the wall. H & E × 934

FIG. 3. The top enlargement showing free-growing cells resembling young fibroblasts, eroding the calcified core of the tubercle. H & E × 934

chronological. Calcification is variable and progresses outward into the capsule, sometimes with a water-marking effect. It is conceivable that diet, vitamin D, etc. may have influence upon its development. Pigmentation is frequently present but it is too indefinite to be of any value in age determination. In any particular case, however, it is of some use, because the extent of pigment is an index of the time required for it to accumulate, with respect to other tubercles in the same patient. Most old tubercles are buried in black "shrouds" of pigmented and emphysematous lung tissue. Hyalinization takes place in old fibrous tissue, especially in large calcified masses, but it is not constant and is accompanied by other more regular changes.

After the bone begins to form, the disintegration goes on indefinitely for life or until the tubercle is entirely resorbed. Without serial X-ray films complete resorption can only be assumed, although it probably occurs more frequently than we now think. The other retrogressive changes have been well described by others (6, 5) or in my other reports, so that there is no need of further elaboration at this time.

A significant fact, so far as age determination and usefulness of the method are concerned, is that most changes take place before fifteen years. In a former study I reported (17) that the average time required from infection to death in endogenous progression was found to be thirteen years, with a latent period of about ten years and a period of clinical activity of three and one-half years. Including a greater number of fatal cases in infancy and childhood would no doubt lower the figure, perhaps near to six or seven years. In a period when it can serve a useful purpose, therefore, reasonable accuracy may be expected and obtained by the age-morphology classification of the tubercles.

A distinct obstacle in applying the principles cited is that certain infections may appear to have different ages due to overwhelming dosage, "overflowing" lesions, reinfections, or transplanted in the form of daughter colonies. Progression of the disease also destroys many lesions.

These various interfering factors will be discussed and shown to cause less disturbance than is apparent from superficial observation.

It is fortunate in this connection to be able to report that in recent work (18) the preponderant majority of tubercles have been found to become sterilized within a relatively short period of time after encapsulation. Although no exact time can be assigned, sterilization seems to occur in practically all small encapsulated tubercles before seven years, the majority by three years and some even within a year after formation. The prolongation of life of the bacilli appears to be most commonly due to their escape through the capsule and an extension around the margin of the tubercle rather than a survival of bacilli within the calcified core. Well encapsulated lesions seem to become sterilized sometime during the second year. After sterilization it is evident that no further extension can take place in the tubercle, as extension can only be caused by living bacilli. In such lesions the progression ceases soon enough to allow age changes to proceed without interruption.

In the rapidly progressive cases, however, it may appear futile to search for

any age characters because they nearly always develop primary cavities. Even less progressive lesions may ulcerate. Ghon (2) reported 36 per cent of primary cavities in his first series of children; Blacklock (3) about 67.0 per cent, and Pagel (19), in Lubarsch-Henke's Handbook, reports a wide variety of percentages from different authors. Many patients survive with the cavities persisting for many years—even decades—as residual primary cavities, to cause an exacerbation after long intervals. Up to the present time there is no accurate method of determining the age of cavities so it is necessary to look for other means of analysis of age factors. In practically all such cases there are lymph node lesions in anatomical relation to the primary focus formed at the same time or soon afterwards, which can give an approximate "time table" of events. In addition isolated parenchymal "satellite" foci may also be present.

Lesions that have been encroached upon by a progressive process can be given only an age rating in proportion as definite criteria remain.

Many lesions are destroyed completely or excavated. but when a painstaking search is made, as was done in the work reported in the book, there is usually such an abundance of data that an age rating can be worked out in all but a small minority of cases.

Of less certainty are the slowly progressive lesions that constantly "overflow" and reveal no definite age character at any one time, although relatively few, they are important because of their danger. Several types have been observed—those that overflow around the borders, those that break through the capsule at one place as "budding" tubercles, and those that set up independent colonies outside the capsule. They are perhaps one of the main causes of the perpetuation for long intervals of living tubercle bacilli in the body. The bacilli work their way out between the cells in the capsule and set up colonies in the outer capsule of the tubercle. Signs of activity may be detected by the presence of monocytes, giant cells and positive cultures. If progression continues long enough and an intervening accident occurs, as Krause (20) has pointed out, an exacerbation will result. It may become a soft infiltrate of an overflowing character that will ulcerate within a few months to many years afterwards. It may stop and heal at any stage of development or may form into huge masses (round infiltrates, "Albert foci" (21), etc.), most of which gradually heal months and years afterwards. The nature of the overflowing types and methods of differentiating them from ordinary lesions will perhaps be clarified by the following illustration.

Case 3: A1116 was a 26.4 year old American female, married at twenty. There was nothing eventful in her history. The onset of her disease was with a cough in March, 1935, three years before her death. In April and May, 1935 she took a strenuous automobile trip to Florida and was very much fatigued afterwards. In October, 1935 she was X-rayed and was told she had an abscess, but soon her sputum was found positive for tubercle bacilli and she was admitted to the Sanitarium. She was put to bed on modified rest regimen and after two months felt much better. In November pneumothorax was begun on the right side, but was discontinued because of adhesions. She died in March, 1938.

One of the larger tubercles overflowing into a bronchus was shown in the book (1), page 228, figures 1, 3 and 4. Another similar but larger tubercle will now be described showing the detailed pathogenesis of the process, as well as various other interesting phenomena (see plate III). In the subapical region there were many smaller tubercles with more perfect capsules, most of which were partly healed. The massive tubercle to be described was almost in the centre of the lung, more anterior to the others. In fact, as will be described later, there was a tendency for the tubercles to progress as they were located forward and downward in the lung.

The lesion is shown in plate III. There was a small calcified nucleus in the upper (anterior) aspect of the tubercle, a heavy wall on the upper side, but nothing but a caseous mass below. There were remnants of collagenous fibres at intervals downward. Then another calcified area on the right indicates a slight pause in the progress of the process, then a lesser one in the left, and then wave on wave of collagen downward to the tip of the tubercle. These alternating waves of collagen (shown clearly with collagen stains) perhaps indicate temporary arrests while the lesion was enlarging. There were also certain areas shown by elastica stain, where complete destruction of all tissue elements resulted. Other areas showed a few broken fibres, others intact blood vessels, others even the outlines of the alveoli. This variability within tubercles is a characteristic of practically all of them and perhaps reveals the changing of the intensity of the action of the bacilli from one time to another and from one colony of bacilli to another. Around the recently formed margins were large numbers of giant cells, between the caseation and the layer of fibres, the monocytes were also frequently found in this same zone of tissue. Acid-fast stains did not reveal acid-fast bacilli, but suspicious granules were present. (Plate III.)

As may be observed, these lesions are easy to identify and offer little difficulty, not only because of their character but also because of their relative rarity. While it is impossible to determine their age, associated lesions may assist in solving the relationships.

The other types of endogenous spread occur where the bacilli pass completely outside the capsule and develop into new tubercles in the outer capsule or outside the tubercle entirely. This may occur in either the parenchyma or lymph nodes. By a careful study of all lesions as to character, position, relation to blood and lymph streams and bronchi, all but a minority of them may be satisfactorily accounted for. Almost invariably when such progression occurs, the age character of the lesions decreases in the direction of the progression. The mechanism is at present only partly known, because complete serial sections are necessary to prove each case. In the lung parenchyma the majority of lesions in the apical and subapical regions follow patterns similar to those described by Loeschcke (22) and descend by the bronchial routes. If the lesions are in the base the first metastases are usually found in the subapical regions. In the lymphatics the metastases take place either progressively towards the blood stream or retrogressively in the case of blockage up to the peritracheal nodes, or down through the diaphragm to the peripancreatic nodes, as shown on other occasions (23) and in chapter VIII of the book (1). When a series of lesions, therefore, from a very old type to a young type occurs in progressive age sequence, the mechanism is probably the insidious progression just described.

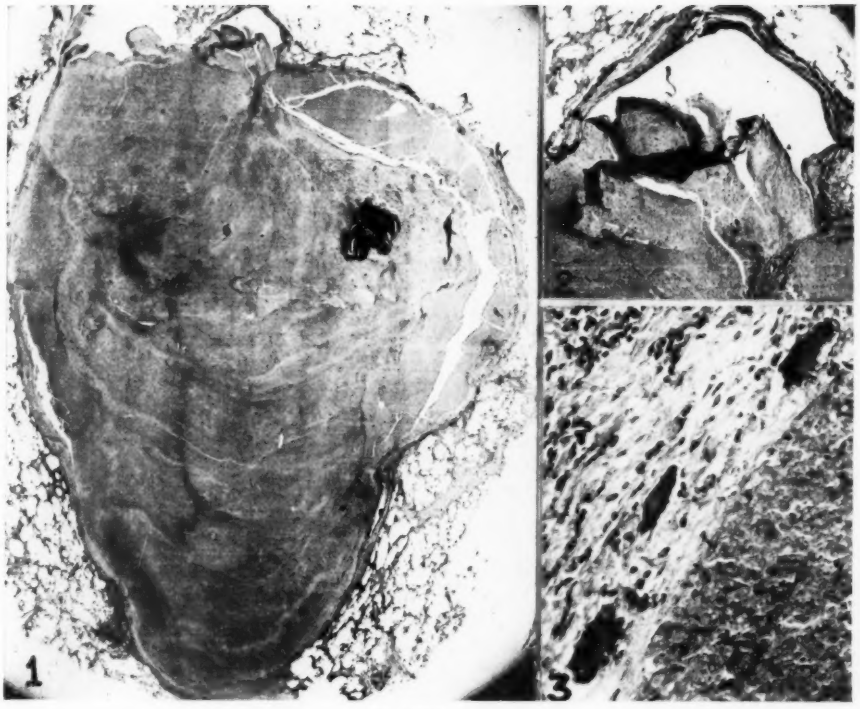


PLATE III

FIG. 1. Tuberculoma in the upper part of right lung of case 3. Note the centres of calcification where there seemed to be a temporary pause in the progress of the infection. Note also the wave effect of fibrous tissue extending towards the tip. H & E × 6

FIG. 2. Apparently the original focus at the top of figure 1. H & E × 15

FIG. 3. Margins of the lesion towards the tip revealing giant cells and a spreading of the lesion. No acid-fast bacilli were found in the lesions, but suspicious granules were present. H & E × 234

When lesions become encapsulated and heal from the same shower of bacilli, they remain remarkable similar in appearance. This has been shown in a separate study (23) where as many as a hundred lesions in the spleen were studied and all were almost identical to each other and also similar to lung and lymph node lesions from which they originated.

It may be observed, therefore, that there are relatively few instances where an age-morphology interpretation cannot be given and the course of the disease followed. When studied with all collateral data and in the light of some associated laws and principles of infection, resistance and pathogenesis, the problems become even more simplified. Some of these collateral factors will now be considered.

There are many conceivable circumstances which may properly be suspected of having a bearing on the aging of lesions. Some of these include dosage and virulence of the bacilli; immunity and allergy of the host; changes in circulation; variations in diets; differences in race, age and sex; induced pneumothorax; associated diseases, etc. While they all play a rôle, none singly or all together seem to change tubercles outside of the limits of biological variation which were clearly laid down in the preface of the book. If there is undue influence of one factor, it seems to be offset by opposing factors and all together appear to be of the order of minor episodes in the whole healing process.

In this type of work all available factors must be made use of, including clinical, antemortem and postmortem studies, X-ray and laboratory findings, with a careful section study.

In addition, all lesions have been interpreted as far as possible in the light of the various principles by which the tuberculous infection carries on in the body. First should be mentioned the Parrot law of similar adenopathies and its counterpart Cornet's law of lymphatic progression. This is very important, because lymph node lesions in series along a given lymphatic channel are in all probability of the same process. They may not all be the same age character, however, as has been explained before.

The law of probability is also worthy of keeping in mind. By it the aerogenous localizations should occur in the same proportion as is found in the mechanical aeration of the lung tissue. This perhaps actually true only in infants where there is little power to resist infection. In people with added resistance or "immunity" smaller doses of bacilli may conceivably be killed, suppressed, expelled by mechanical action, or shunted into the "eddies" of inactive bronchi where they may be killed off or all too often develop into foci of infection. The lack of clearing of the subapical bronchi would retain such errant bacilli, as well as others coming in from without. It is conceivable that this fact may be responsible for the predilection of this region of lung for so many reinfections as well as for the normal quota of primary infections.

What may not be classed as laws, yet there is enough evidence to class them as plausible hypotheses, are the theory of *localization of infection* and the theory of disease *progression*. They are discussed together for they are virtually reciprocal and the more easily understood when discussed together.

In the former the lesions seem to locate in the parts of the lung having the

least motility. The most important localization is that of bronchogenic lesions in the subapical regions. The first suggestion of this localization was by Fowler (24) and then Ewart (25) and then many others more recently. Lateral view roentgenograms, as well as anterior-posterior views assist in interpretation. The principle was also demonstrated in a former work with regard to "primary" ulcerations (26) appearing in roentgenological examination. Braeuning (27) recently amplified this idea with respect to early localization of bacilli, showing that there were almost as many localizations in the apex. The difference seems to be that those in the apex are more benign (28). The extension of the disease from the subapical region is forwards and downwards, taking in the true apex (29) and the apices of the lower lobes, then continuing on in the same antero-caudal direction until all lung tissue is involved or until death ensues. The literature on this phase of the subject is extensive but enough has been cited to show the trend.

Another useful hypothesis is the apico-caudal progression of haematogenous lesions. As pointed out by Braeuning and Redeker (30) and Lydtin (31), haematogenous lesions localize in the apical regions first (slightly more to the right), perhaps because of sluggish blood circulation, and progress gradually towards the bases (30). Isolated regional disseminations claimed by Huebschmann (5), if present at all, are the exception. The sluggish flow of lymph may also contribute to the slow progress, as contended by Tendeloo (32). On the contrary, the more rapid extension downward and forward after infection may conceivably be facilitated by the motility of the bronchi augmented by the increased flow of blood and lymph and perhaps ciliary action on those regions.

Occasionally there are types of infection which lend themselves well to illustrate these principles. These are the cases in which a massive generalization occurred in the lungs without a meningitis, so that a survival of several months is possible. Case 2 of this series is an excellent example. There was a progressive increase in size and character from the subapical region to the lower anterior region from fibroid lesions 1 to 2 mm. in size to exudative lesions 1 to 2 cm. with early ulcerations and tendency to spread by bronchial routes. It forms a corollary, therefore, to the subapico-caudal progression theory.

Finally the principle of increased resistance to reinfection by an existing infection is worthy of bearing in mind. It has been shown repeatedly that infected animals are difficult to reinfect, and when they are infected the dosage required is larger than for a first infection. This is particularly useful in arriving at conclusions regarding endogenous and exogenous reinfections. Graeff (33) and Redeker's (34) theory of "trigger action" in which an exogenous reinfection will cause an exacerbation of an existing infection, is of doubtful merit since it assumes that small exogenous doses will cause an exacerbation of bacilli already adapted to living on the tissues and perhaps of larger dosage.

The listing of the various principles mentioned is merely to illustrate how a more logical interpretation may be assigned to the majority of lesions and even to the rarer lesions that are occasionally met with. Infections "out of position" or "out of relation" to other lesions in any series coming under the above men-

tioned laws and hypotheses are subject to careful scrutiny. Of course, a few infections do not lend themselves to study at all, and a vast number of lesions are likewise not amenable to such an analysis. Most infections, however, reveal enough so that they may be interpreted readily as to their approximate age and the probability of an endogenous or exogenous origin.

Outside of the localization in the lung, the time of infection and perhaps age characteristics, there is little basic difference in tubercles. The most significant factor is the widely variable allergy present. Exogenous reinfections are bound to occur as frequently as the primary infections. If the rate for first infections is 1.5 per cent a year, there must be also the same for reinfections. The same number of "takes" however, need not and perhaps do not occur. After the"take" occurs, then the tubercle formation may go on as in any infection, but is modified by the previous infections with the tubercle bacillus and perhaps also certain nonspecific factors. This "allergic" or "changed reaction," therefore, is not always due to "allergy" alone as many other factors also enter in (Corper (35) and Birkhaug (36). Allergy does seem to play the dominant rôle and tends to give the infection its recognized reinfection character. Certainly the more the allergy the more changed is the reaction and the farther it is removed from a "type" or "primary" tubercle.

The great majority of "reinfects," however, maintain a close similarity in morphology if not age characteristics, as well as to primary lesions. Those that do not are the ones that are formed by large dosage of bacilli; rapidly overflowing types that form acinous tubercles; or large infiltrates that ulcerate. All tubercles that remain static seem to undergo changes not greatly unlike those of primary tubercles, even if they may not prove to have the same chronological aspects. Not infrequently, perhaps even commonly, there are reinfections simulating the primary complex. Schürmann (7) and especially Terplan (37) have described the "reinfection complex." It is not only an established fact but also one supported by strong probabilities. It is difficult to be certain as the ages approximate each other. No doubt many of these are virtually primary lesions, because the true primary was so slight that it caused little basic change in the host. The only reason they are not accepted readily is because of the difficulty in proving their true nature. With the application of the age-morphology pattern to tubercles, it will help to recognize more of these infections.

The majority of reinfections, however, are no doubt isolated foci that do not form a lymph node "complex" and are not related to former lesions in position or age and may be studied as a special group.

By a careful and complete method of study, therefore, the majority of primary lesions and many reinfection lesions may be studied rather accurately by the methods proposed. Surely the results so far justify the efforts spent.

SUMMARY

A review of the work on the age-morphology of primary tuberculous foci has been reported together with a few illustrations to emphasize certain important features.

An important fact is that most primary tubercles soon become sterile and regressive. As they become static, they go through chronological changes that are sufficiently constant so that they can be used as age markings. Healed lesions of the same age are remarkably similar during the first fifteen to twenty years of their existence. In rapidly progressive lesions there are usually isolated satellite foci that become encapsulated in spite of the progression. There are also occasionally found more slowly progressive "overflowing" lesions, but they do not produce any serious interference with the age analysis, due to several reasons, principal of which is their relative scarcity. "Overflowing" lesions, reinfection lesions, "reinfection complexes" and other special types of lesions are discussed and means of studying them are suggested.

Among the most important collateral data for the study of the age of tubercles is a thorough study of the clinical, X-ray and laboratory features of cases in the light of the laws of the disease progression in the body.

The relationship of morphology to age of tubercles appears not only to be a reality in the majority of tubercles, but seems to afford interesting possibilities with respect to studying progression of the disease in the body.

SUMARIO

Preséntase un repaso de los trabajos relativos a la morfología-edad de los focos tuberculosos primarios, junto con algunos ejemplos para hacer hincapié en ciertas características importantes.

Un punto importante es que la mayor parte de los tubérculos primarios pronto se vuelven estériles y regresivos. A medida que se vuelven estáticos, sufren alteraciones cronológicas que alcanzan suficiente constancia para poder ser utilizadas como signos cronológicos. Las lesiones cicatrizadas de la misma edad son notables por su semejanza en los primeros quince a veinte años de su existencia. En las lesiones rápidamente evolutivas suele haber focos satélites aislados que se encapsulan a pesar de su progreso. Se encuentran también de cuando en cuando lesiones "rebosantes" de avance más lento, pero no afectan mayor cosa el análisis cronológico debido a varias razones, de las cuales la principal es su escasez relativa. Discútense estas lesiones "rebosantes," las lesiones de reinfección, los "complejos de reinfección" y otros tipos especiales de lesiones y se proponen medios de estudiarlas.

Entre los datos colaterales más importantes para el estudio de la edad de los tubérculos figura el estudio detenido de las características clínicas, roentgenológicas y de laboratorio de los casos a la luz de las leyes del progreso de la enfermedad en el organismo.

La relación de la morfología con la edad de los tubérculos parece no tan sólo ser una realidad en la mayoría de los últimos, sino también ofrecer posibilidades interesantes con respecto al estudio de la evolución de la enfermedad en el organismo.

REFERENCES

(1) SWEANY, H. C.: Age Morphology of Primary Tubercles, Springfield, Illinois, C. C. Thomas, 1941.

(2) GHON, A.: Primary Lung Focus of Tuberculosis in Children, London, 1916.
(3) BLACKLOCK, J. W. S.: Tuberculous Disease in Children, London, 1932.
(4) LANGE, M.: Der primäre Lungenherd bei der Tuberkulose der Kinder, Ztschr. f. Tuberk., 1923, *38*, 263.
(5) HUEBSCHMANN, P.: Pathologische Anatomie der Tuberkulose, Berlin, 1928.
(6) JAFFÉ, R. H., AND LEVINSON, S. A.: Histological studies on healed tuberculous primary lesions of the lung, Am. Rev. Tuberc., 1929, *20*, 214.
(7) SCHÜRMANN, P.: Der Primärkomplex Ranke's unter den Anatomischen Erscheinungsformen der Tuberkulose, Virchow's Arch. f. path. Anat., 1926, *260*, 664.
(8) PUDER, S.: Kalkherde im menschlichen und tierischen Organismus unter besonderer Berücksichtigung der Tuberkulose, Zentralbl. f.d. ges. Tuberk.-Forsch., 1932, *36*, 177.
(9) GRETHMANN, W.: Zur Pathologie der akuten disseminierten Miliartuberkulose der Lungen, Beitr. z. Klin. d. Tuberk., 1928, *71*, 1.
(10) TERPLAN, K.: Book review, Am. Rev. Tuberc., 1941, *44*, 490.
(11) SWEANY, H. C.: Observations in multiple calcifications, Ibid., 1935, *32*, 73.
(12) PAGEL, W.: Die allgemeinen pathomorphologischen Grundlagen der Tuberkulose, Berlin, 1927.
(13) ASCHOFF, L.: Über die natürlichen Heilungsvorgänge bei der Lungenphthise, München, 1922.
(14) SWEANY, H. C.: Factors of healing, latency and progression in pulmonary tuberculosis, Am. Rev. Tuberc., 1939, *39*, 348.
(15) SWEANY, H. C.: Pathogenesis of pulmonary tuberculosis, Journal-Lancet, 1933, *53*, 393.
(16) SWEANY, H. C., TILLOTSON, A. E.. AND KOZIELEK, V.: Studies on the retrogressin changes in tubercles, Am. Rev. Tuberc., 1938, *37*, 484.
(17) SWEANY, H. C.: The tuberculosis problem viewed in the light of recent pathologic studies, Minnesota Med., 1939, *22*, 595.
(18) SWEANY, H. C.: Unpublished data.
(19) PAGEL, W.: Die einzelnen pathologisch-anatomischen Erscheinungsformen der Lungentuberkulose, In Lubarsch-Henke, Handbuch, III/2, 190–219.
(20) KRAUSE, A. K.: Environment and Resistance in Tuberculosis, Baltimore, 1923.
(21) ALBERT, A.: Mehrfache tuberkulöse Rundinfiltrate, Beitr. z. Klin. d. Tuberk., 1931, *78*, 647.
(22) LOESCHCKE, H.: Development, cicatrization and reactivation of pulmonary tuberculosis in adults, Ibid., 1928, *68*, 251.
(23) SWEANY, H. C.: On the nature of calcified lesions: with special reference to those in the spleen, Am. J. Roentgenol., 1940, *44*, 209.
(24) FOWLER, J. K.: Localization of the Lesions of Phthisis in Relation to Diagnosis and Prognosis, London, 1888.
(25) EWART, W.: Pulmonary cavities, their origin, growth and repair, Brit. M. J., 1882, *1*, 333, 369, 415, 452, 492.
(26) SWEANY, H. C., COOK, C. E., AND KEGERREIS, ROY: A study of the position of primary cavities in pulmonary tuberculosis, Am. Rev. Tuberc., 1931, *24*, 558.
(27) BRAEUNING, H.: Einige Feststellungen über den Beginn der Lungentuberkulose des Erwachsenen an Serien von Roentgenphotographien vom normalen bis zum krankhaften Befund, Ztschr. f. Tuberk., 1932, *64*, 416.
(28) KAYSER-PETERSEN, J. E.: Die Bedeutung der Lungenspitzen-tuberkulose für die Entstehung der Schwindsucht der Erwachsenen, Beitr. z. Klin. d. Tuberk., 1928, *70*, 132.
(29) DOUGLAS, BRUCE H., PINNER, MAX, AND WOLEPOR, BEN: Acute subapical versus insidious apical tuberculosis, Am. Rev. Tuber., 1929, *19*, 153.
(30) BRAEUNING, H., AND REDEKER, F.: Die haematogene Lungentuberkulose, ihre Entstehung und Rückbildung, ihre Frühund Spätentwicklung zur Phthise, Tuberkulose-bibliothek #38, 1931.

(31) LYDTIN, K.: Haematogene und bronchogene Formen der Lungentuberkulose, Tuberkulose-bibliothek #45, 1932.

(32) TENDELOO, N. P.: Die Tuberkulose der Lungenspitze und das "Frühinfiltrat, Krkh.-Forschg. 6, 1928.

(33) GRAEFF, S.: Pathologische Anatomie der beginnenden Lungenphthise, Zentralbl. f.d. ges. Tuberk-Forsch., 1928, *29*, 389.

(34) REDEKER, F.: Über die infraclaviculären Infiltrate, ihre Entwickelungsformen, ihre Stellung zur Pubertätsphthise und zum Phthiseogenese-Problem, Beitr. z. Klin. d. Tuberk., 1926, *63*, 574.

(35) CORPER, H. J., AND COHN, M. L.: Intoxication in tuberculosis, Am. Rev. Tuberc., 1940, *41*, 71.

(36) BIRKHAUG, K.: Allergy and immunity in experimental tuberculosis, Acta tuberc. Scandinav., 1937, *11*, 25.

(37) TERPLAN, K.: Anatomical Studies on Human Tuberculosis. VII. True reinfection with a typical tuberculous complex (Ranke); VIII. Progressive tuberculosis with a tuberculous complex of true reinfection; IX. Intestinal complex of recent exogenous reinfection, Supplement to Am. Rev. Tuberc., August, 1940.

BRIEF NOTES

TUBERCULOSIS IN A CARCINOMA OF THE OESOPHAGUS[1]

DAVID T. CARR AND DAVID M. SPAIN

Tuberculosis of the oesophagus may originate in a variety of pathways. Lockhard in a comprehensive review of the literature in 1913 found 69 acceptable cases of tuberculosis of the oesophagus which he classified into the following groups on the basis of their pathogenesis:

1: Direct implantation of bacilli following trauma to the oesophagus
2: Direct implantation of bacilli in a carcinomatous ulceration of the oesophagus
3: Direct implantation of bacilli without a previous lesion of the oesophagus
4: Extension from the larynx or the pharynx
5: Extension from vertebral caries
6: Extension from caseous mediastinal lymph nodes
7: Haematogenous infection
8: Unclassified

Despite these many potential pathways, tuberculosis of the oesophagus is very rare. Lockhard found that there were only 15 cases of tuberculosis of the oesophagus in a series of 16,489 autopsies on tuberculous subjects. Considering the habitual swallowing of infectious discharges by phthisical persons, this low incidence may be accounted for in part by such protective mechanisms as the squamous cell lining of the oesophagus, its tubular structure without crypts or pockets in which bacilliferous exudate might stagnate and the frequent and forceful flushing by food, drink and saliva which prevents prolonged contact of infectious material with the mucosa.

In the last ten years there have been over 1,400 autopsies on tuberculous patients at Bellevue Hospital. Only one of these was found to have tuberculosis of the oesophagus. The mechanism of infection in this case was implantation of bacilli in a carcinomatous ulceration of the oesophagus.

CASE REPORT

The patient, a forty-two-year-old Negro male, was admitted to the Tuberculosis Service of Bellevue Hospital on October 11, 1940 because of cough productive of blood-streaked sputum, fever, night sweats and progressive weakness. There had been some anorexia and generalized abdominal cramps with a loss of twenty pounds in weight, but no dysphagia.

Physical examination revealed an acutely ill, dehydrated Negro male with a temperature of 97°, pulse rate of 70 and respiratory rate of 22. Pediculi were found in the scalp. The teeth were carious. There were dulness, broncho-

[1] From the Tuberculosis Service of the First Medical Division of Bellevue Hospital and the Department of Practice of Medicine, Columbia University, College of Physicians and Surgeons, New York, New York.

vesicular breath sounds and many râles in the upper part of the lungs. The heart was normal. Blood pressure was 150/80. The lower half of the abdomen was tender.

The roentgenogram of the chest revealed extensive bilateral caseocavernous pulmonary tuberculosis, more marked on the right. Microscopic examination of the unconcentrated sputum showed acid-fast bacilli. The erythrocyte count was 1,790,000 with 50 per cent haemoglobin. The leucocyte count was 16,400, 84 per cent of which were polymorphonuclear neutrophils. The blood Wassermann test was negative. Urine analysis revealed a specific gravity of 1.010, a trace of albumin and a very few granular casts; no acid-fast bacill were found. The blood nonprotein nitrogen was 108 mg. per cent, and the phe

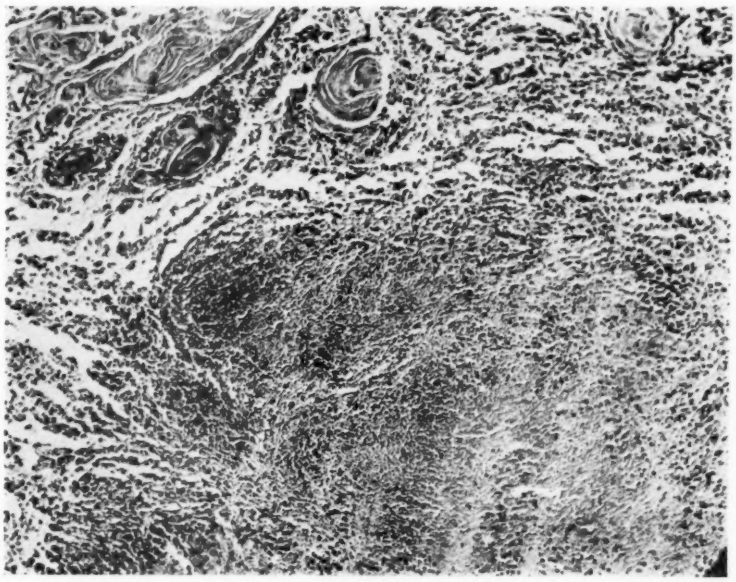


FIG. 1. Caseous tuberculosis surrounded by epithelial pearls in wall of oesophagus Haematoxylin & Eosin × 10.

nolsulphonphthalein test showed 5 per cent excretion at the end of two hours. He remained acutely ill, gradually became comatose and died on the twenty-seventh hospital day.

Necropsy: Postmortem examination revealed bilateral fibrocaseous pulmonary tuberculosis with multiple cavities and a lobular distribution of caseous nodules. The hilar and mediastinal nodes were slightly enlarged, soft and grayish-yellow in color. A pale, shallow, solitary, irregularly oval, longitudinal ulcer 2 x 3 cm. in size was found in the midportion of the oesophagus on its anterior wall. The base of this ulcer was granular and grayish-yellow; the edges were slightly raised and showed a minimal amount of undermining. The wall of the oesophagus in this region was moderately thickened, but the external surface was smooth throughout and free of adhesions. There were no lymph nodes in the immediate

vicinity of the ulcer. Several shallow ulcers were present in the terminal ileum and ascending colon. The kidneys were irregularly scarred and somewhat reduced in size. On section the cortices were narrowed. None of the other findings were of abnormal significance.

Microscopical examination of the oesophagus revealed an ulcer consisting of neoplastic squamous cells which invaded the muscularis. Numerous epithelial pearls were present. Within this malignant area was a tubercle consisting of a large caseous necrotic centre and surrounded by several epithelioid cells, lymphocytes and an occasional Langhan's giant cell (figure 1). The tubercle was limited to the area of ulceration and extended from the ulcerated surface down to the muscular coat. On all sides the tubercle was surrounded by neoplastic tissue. No evidence of tuberculosis was found elsewhere in the oesophagus. The other microscopical findings substantiated the naked-eye diagnosis of bilateral fibrocaseous tuberculosis with cavitation, squamous cell carcinoma of the oesophagus with secondary tuberculous implantation, tuberculous ulcers of the ileum and ascending colon and chronic pyelonephritis with arteriolar nephrosclerosis.

DISCUSSION

A review of the literature has revealed 5 additional cases of carcinoma associated with tuberculosis of the oesophagus. Zenker, Cordua and Weyeneth each reported autopsy findings of carcinoma of the oesophagus with a more recent tuberculous infection. Pepper and Edsall reported an autopsy which showed tuberculosis to have been present longer than the carcinoma. Dean and Gregg reported a case proven clinically by an oesophagoscopic biopsy but they were unable to tell which disease was the older one. On the basis of a positive blood Wassermann and the relief of dysphagia by antiluetic therapy, the additional diagnosis of syphilis of the oesophagus was made. Unfortunately no follow-up record of this case is available.

In our case the failure to find haematogenous tuberculosis elsewhere in the body rules against the possibility of a haematogenous origin for the tubercle in the oesophagus. The absence of tuberculous lymphadenitis and of peri-oesophageal adhesions or scarring points against a direct lymphatic extension. The anatomical relationship of the tubercle to the malignant ulcer as described above indicates that the tubercle was secondarily implanted on the malignant tumor as a result of swallowed exudate laden with tubercle bacilli.

SUMMARY

A patient is reported showing the rare combination of tuberculosis engrafted upon a squamous cell carcinoma of the oesophagus.

SUMARIO

Preséntase un enfermo que revela la rara combinación de tuberculosis injertada en un carcinoma celuloescamoso del esófago.

We wish to express our gratitude to Dr. J. Burns Amberson, Jr. for suggestions and criticisms aiding the preparation of this report.

BIBLIOGRAPHY

(1) LOCKARD, L. B.: Esophageal tuberculosis: A critical review, Laryngoscope, 1913, *23*, 561.
(2) ZENKER: Quoted by LOCKARD.
(3) CORDUA: Quoted by LOCKARD.
(4) WEYENETH: Quoted by LOCKARD.
(5) PEPPER AND EDSALL: Tuberculous occlusion of the esophagus with partial cancerous infiltration, Am. J. M. Sc., 1897, *114*, 44.
(6) DEAN, L. W., AND GREGG, J. B.: Report of case of coexistent carcinoma, tuberculosis and syphilis of the esophagus, Ann. Otol., Rhin. & Laryng., 1917, *26*, 819.

EFFECT OF PREGNANCY UPON TUBERCULIN REACTION

RAYMOND W. CONN[1]

In the voluminous older literature on the subject of tuberculosis and pregnancy there may be found many references to a supposed decrease in resistance to this infection during pregnancy. In support of this opinion certain workers have reported a loss of tuberculin sensitivity during pregnancy. For instance, Nobecourt and Paraf (1) reported that 15 to 20 per cent of gravid women lose their tuberculin sensitivity during the last trimester. Other workers generally report a somewhat higher percentage, as for example, Stern (2), who reports that over 50 per cent of the tuberculin sensitive women lost reactivity during the last trimester.

This subject bears also upon the problem of endocrine influences on allergic states. The great hormonal changes that ensue with pregnancy are well known. In line with this idea are the reported alterations in tuberculin sensitivity at puberty, the menses or at the menopause, a marked decrease of, or loss of sensitivity having been noted at these times (3).

METHOD

For several months all new admissions to a municipal prenatal clinic were skin tested by intracutaneous injection of 0.1 cc. of Old Tuberculin 1:1,000 dilution, prepared by the Michigan Department of Health. All reactors were retested if possible on one or more subsequent visits. Retesting was done as far along in the last trimester as possible. All the members of this group were examined clinically and roentgenographically for evidences of tuberculosis and were found to be free from any active lesions.

RESULTS

Of the 150 women tested, 90, or 60 per cent, were found to react. Of this group of 90, we were able to repeat tuberculin tests on 41. On some patients the test was repeated only once, on others twice. In each case the test was repeated as close to term as possible.

Of these 41 cases there were only 2 clear cut instances of loss of sensitivity, one in a thirty-eight year old white female and the other in a twenty year old colored female. A twenty-four year old female, who had reacted positively in her fifth month of pregnancy, gave a mild, questionably positive reaction in her seventh month of pregnancy.

DISCUSSION

It is true that from as small a series as is here presented no conclusion may be drawn with finality. Perhaps 3, or 7 per cent, of the group of women whom we were able to check for possible loss of tuberculin reactivity in the latter part of

[1] 408 Fox Theatre Building, Detroit, Michigan.

pregnancy did show such a loss. However, we do believe that this series does demonstrate that such a decrease of tuberculin allergy certainly is not a constant, or even frequent phenomenon in pregnancy. Further conclusions must await the accumulation of more data.

SUMMARY

One hundred and fifty pregnant women were tuberculin tested early in pregnancy and 90 of these reacted positively. Of the 90, 41 were available for follow-up study. It was found that 38, or 93 per cent, definitely retained tuberculin sensitivity. Two patients lost their sensitivity in the last trimester and another patient showed only a very slight reaction in the last trimester. It is thought that the loss of tuberculin sensitivity in pregnancy is not a frequent occurrence.

SUMARIO

Ciento cincuenta gestantes fueron comprobadas con tuberculina al principio del embarazo, y 90 reaccionaron positivamente. De las 90, pudo seguirse a 41, descubriéndose que 38 (93 por ciento), retenían netamente la sensibilidad a la tuberculina. Dos enfermas perdieron su sensibilidad en el último trimestre, y otra reveló únicamente una reacción muy leve en el último trimestre. Según parece, la pérdida de sensibilidad a la tuberculina en el embarazo no es frecuente.

The author wishes to express his appreciation to Dr. Bruce H. Douglas for his kindly interest and guidance in this work.

REFERENCES

(1) Cited by JAMESON in text, Gynecological and Obstetrical Tuberculosis.
(2) STERN, ROBERT: Ztschr. Geburtsh. u. Gynäk., 1910, *66*, 532.
(3) COULARD, E.: Quoted by RIST, Brit. M. J., 1927, *2*, 247.

A PORTABLE X-RAY UNIT FOR FIELD STUDIES IN TUBERCULOSIS[1]

JOSEPH D. ARONSON AND ROBERT M. SAYLOR

The importance of roentgenological examinations of the chest in the detection of tuberculosis is well recognized. Unfortunately it is impossible to conduct such examinations in places where electric current is not available or when the voltage and frequency of the cycles are not suitable for operating the X-ray unit.

In the course of some studies, dealing with the incidence of tuberculosis among Indians living in the United States and in Alaska, it was necessary to examine, roentgenologically, a representative cross section of the population. In many instances no electricity was available in the villages which were often situated many miles from the nearest hospital. It was therefore necessary to design a mobile X-ray unit and motor generator which were compact, relatively light in weight, dependable, economical, which would withstand the wear and tear incident to travel over all types of roads and trails, and with the exception of the motor generator, could be transported in a small plane.

The unit which was assembled (figure 1) consisted of a three-quarter ton Chevrolet Carryall type of car, geared for four speeds and equipped with oversize tires. A self starting gasoline powered motor generator weighing about 450 pounds was bolted to two pieces of heavy lumber and these in turn were bolted to the floor of the car, immediately back of the front seat. The motor generator of 60 cycle frequency had an output of 3,000 watts, 115 volts, 26.1 amperes. The gasoline required for the operation of this unit was obtained by running an auxiliary line from the main supply line of the automobile motor. This branch line was made rigid so that vibration would not cause the line to leak or break. It was advisable to fasten the batteries, enclosed in a case, to the floor of the car and to keep the radiator of the motor generator filled at all times with ethylene glycol. The electric output of the unit could be determined at any time by means of a voltmeter and ammeter readily mounted on the inside wall of the car. The electric current was transmitted from the motor generator, through an armored cable running beneath the floor, to a covered outlet installed in the floor of the car. The X-ray unit was connected to this outlet by means of a 100 foot section of heavily insulated copper wire which was carried on a reel mounted inside the car. The X-ray head and control units were carried on air foam rubber cushions in order to minimize the danger of damaging the X-ray unit. During the first year this car and equipment were driven over 20,000 miles on all types of roads without damaging any part of the equipment.

The X-ray unit used in our studies was a 15 MA portable type of machine which used 1,900 watts, and which at a distance of 30 to 36 inches from the chest produced readable films after an X-ray exposure of one-fourth to one-half second. This unit was carried in three boxes weighing 31, 44 and 45 pounds respectively.

[1] From the Office of Indian Affairs, Department of the Interior, Washington, D. C., and The Henry Phipps Institute, University of Pennsylvania, Philadelphia, Pennsylvania.

FIG. 1. Car equipped with portable X-ray unit

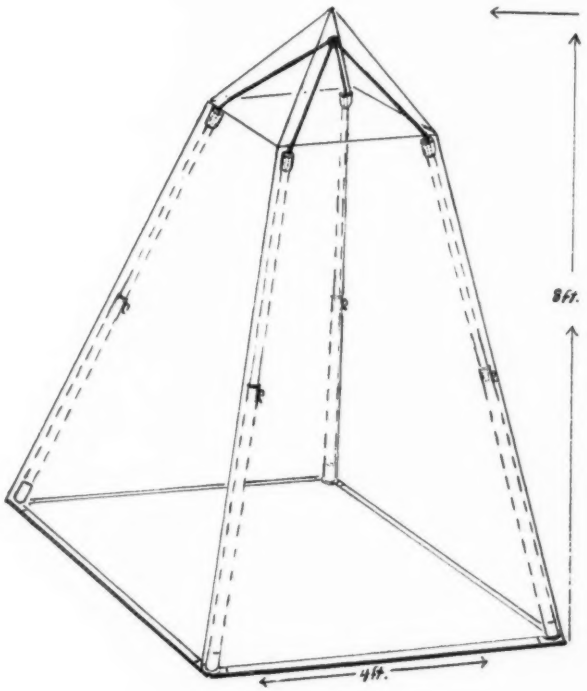


FIG. 2. Dark room

To facilitate the loading and unloading of cassettes, as well as provide a dark room for developing films, we designed a portable tent modeled after an umbrella type tent (figure 2). This tent measuring 8 feet high at its peak and 4 feet square at the base, was made from two layers of black Byrd cloth. A black canvas floor was sewed to the sides of the tent while the opening into the tent ran its entire height and was closed by means of a zipper which could be manipulated either from inside or outside the tent. The tent was supported by a headpiece of four rods hinged to a central ring and each rod slipped into an upright telescoping pole. To make the tent more rigid, a 1 inch wide, 4 foot long strip of strap iron, hinged like a knife at each corner, was placed on the floor along the inside margin of the tent; an iron knob one-half inch high was fastened to each corner of the strap iron and the upright poles were slipped over this knob. The Byrd cloth covering and canvas floor weighed ten pounds and rolled up into a small bundle. The metal supports weighed about 15 pounds. This dark room was used in Arizona in the open where the light measured 15,000 foot candles or more, and there was no fogging of films.

This tent may be used as a developing room if care is taken to prevent the developing and fixing solutions from coming in contact with the cloth or if the cloth is properly treated so that these solutions will not affect the cloth.

The bulkiness and weight of the developing tanks ordinarily used for the processing of X-ray films makes them impracticable for use under field conditions particularly when they have to be transported in a small plane. To overcome this, three tanks were constructed with a capacity of about 5 gallons, from 24-guage stainless steel. The tanks were made to rest inside one another each measuring a half inch smaller than the one into which it fit. The largest measured $20\frac{3}{4}$ inches high, 5 inches wide and $17\frac{3}{4}$ inches long. A shelf measuring one inch wide was bent so that the film hangers could be arranged on it.

During the course of our investigations in southeastern Alaska we transported all of the X-ray equipment, except the motor generator, in the ordinary four passenger plane. The total weigh of our X-ray unit, developing tanks, cassettes, films, hangers, developer powder, fixing powder, cassette stand, and incidentals ranged from 250 to 275 pounds. At no time have the planes, fitted with pontoons, carrying the pilot, 3 passengers and this equipment, had difficulty in taking off from the water.

The total cost of the car, motor generator, X-ray unit, cassettes, dark room, cable and tanks in 1939 was between $2500 and $3000.

AN IMPROVED STEAM SUCTION APPARATUS[1]

For Intracavitary Aspiration

E. S. MARIETTE

Thompson of Sunnyside Sanatorium has published a description of a method of utilizing the steam heating system as a source of suction for intracavitary aspiration. This is a simple and inexpensive method of securing the suction needed for the treatment of cavities by the Monaldi method and can easily be set up for year-round use in a sanatorium or hospital which has a vacuum return to the heating system and which has equipment such as sterilizers, laundry or kitchen which must be operated the year around.

To facilitate the use of this method of securing suction and to provide for a constant suction which will not vary with any fluctuation in the vacuum system, a suction regulating valve, which can be so adjusted that it will maintain any desired level of suction and which will reduce the air entering the vacuum system to that coming from the patient only, has been developed by Mr. Charles Sampson, head of our Engineering Department. The valve, which was built in our own shop from material which we had on hand, together with an ordinary globe-valve for turning the mechanism on and off and a standard check-valve to prevent a reversal of the flow should something go wrong with the system to convert the vacuum into positive pressure, is shown on figure 1.

The body of the valve is of cast iron $3\frac{3}{4}$ inches in diameter with a cover and a base forming a chamber which is divided into an upper and lower chamber by a thin rubber diaphragm. The air pressure in the upper chamber is kept at atmospheric pressure by means of perforations in the cover. This permits free movement of the diaphragm. The lower chamber has three openings. One leads towards the vacuum system, one is a safety-valve, while the third leads towards the patient.

The one leading towards the vacuum system has a $\frac{1}{8}$ inch vertical opening in the center of the chamber into which the regulating valve stem sets.

The second opening leads downward from the lower chamber and is fitted with a weight with a cone-shaped end which rests over an opening to the outside air. Should the vacuum become too large it will raise the weight, drawing atmospheric air into the chamber. It will thus protect the patient against an excess of vacuum and is called an excess vacuum safety-valve.

The opening leading towards the patient is on the opposite side of the chamber from that leading towards the vacuum system. The metal tube leading from this opening has a $\frac{1}{8}$ inch opening drilled on the upper side. This is covered by a small piece of light weight rubber sheeting, one end of which is fixed while the other end is free and rests over the opening. Should pressure instead of suction develop in this tube it can escape from this opening and thus prevent positive

[1] From Glen Lake Sanatorium, Oak Terrace, Minnesota.

pressure from developing in the cavity. Therefore, it is called an excess pressure safety-valve.

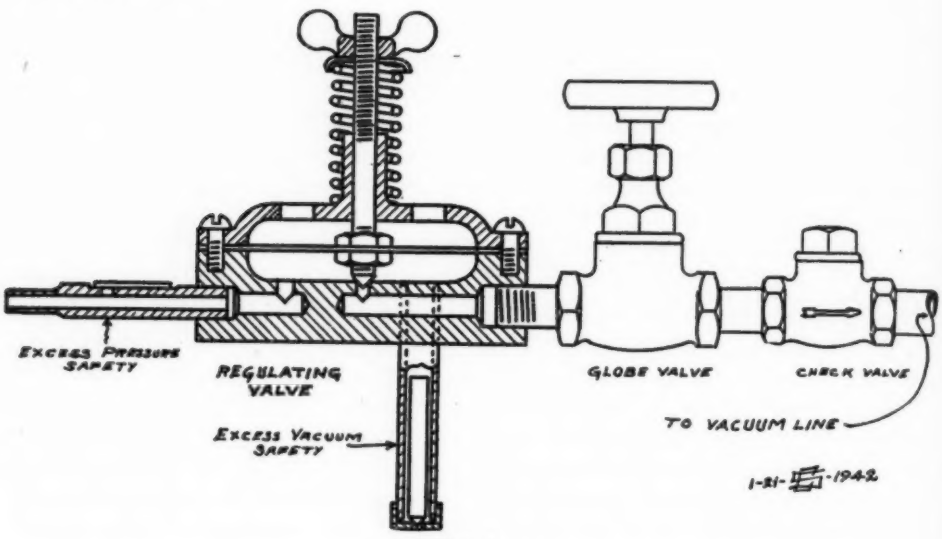


FIG. 1

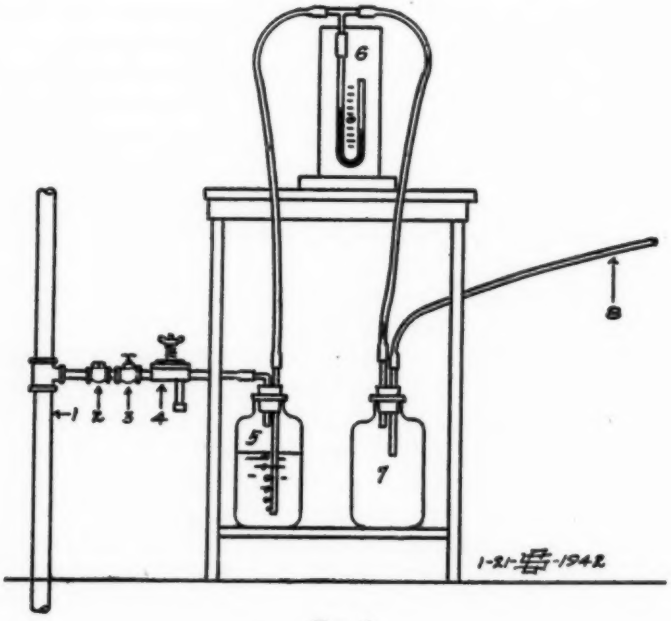


FIG. 2

The diaphragm is made of light weight diaphragm rubber, into the centre of which the suction valve stem is clamped with two thin nuts. The valve is operated by the diaphragm and is guided by a sleeve on the cover. It is kept

open by a spring which rests on the cover and presses upward against the regulating spring nut. The spring itself is made of 16-gage steel in ten coils, ¾ inch in diameter. The free length of the spring is two inches.

After the machine is connected up the suction-valve is adjusted by opening the globe-valve thus allowing some of the air under the diaphragm to be drawn away. The pressure of the atmospheric air on top of the diaphragm at once closes the valve. With this setting the manometer rests at zero. The tension on the spring is then gradually increased until the manometer readings show that the desired amount of suction has been obtained and that a balance exists between the spring tension, the atmospheric pressure over the diaphragm and the amount of vacuum under the diaphragm.

With this type of suction-valve it is possible to maintain a constant suction with a minimum amount of attention from the nurse irrespective of whatever fluctuation may develop in the vacuum system. Also, because of the various checks and valves, the patient is protected against an excess vacuum, should the regulating valve stick, by an opening to the outside which will permit an inflow of atmospheric air. The patient is also doubly protected against positive pressure instead of vacuum in the system: (*1*) by means of a check-valve which permits flow only in one way and is supposed to close should the flow of air be reversed and (*2*) by an excess pressure safety-valve on the tube leading from the suction chamber to the patient. This will blow open and let air escape should the vacuum be converted to positive pressure.

The vacuum system itself is protected against contamination by materials aspirated from the patient through the insertion of a wash bottle containing a solution of one to one thousand bichloride of mercury between the manometer and the regulating valve.

Thus the machine is safe, it is inexpensive, it is positive in action and after once set it requires a minimum amount of attention on the part of the nurse. It is adjustable and any amount of suction that is desired can be obtained. We are advocating it as a source of suction wherever a constant suction is desired such as in superpubic bladder drainage, gastric suction, intracavitary drainage, in fact, wherever suction of an open or closed cavity is needed.

The complete set-up as we are now using it is shown on figure 2. In this sketch number 1 is the vacuum return line from the radiator, which in our system is under ten inches of vacuum. Number 2 is a check-valve so placed that it will close should the vacuum be converted into positive pressure. Number 3 is an ordinary globe-valve which is used as a shut-off valve. Number 4 is the suction regulating valve. Number 5 is the wash bottle containing the bichloride of mercury solution. Number 6 is the mercury manometer graduated into centimeters. Number 7 is the catch bottle and number 8 is the rubber tube to the patient.

We have four of these valves in constant use and have found them very satisfactory. They are not patented but a small service charge will be made for working drawings and blueprints should anyone desire to construct a similar valve for use in his own institution.

LeRoy S. Peters

1882–1941

A Lay Tribute to Dr. L. S. Peters

"Pete was the most unselfish doctor, the most unselfish man, I ever knew," said a veteran associate.

To his tuberculous patients, Doctor Peters was a jovial, sympathetic soul with unlimited time for a long breezy chat at one p.m. or one a.m., if the patient needed it. One night after a party he was driving me home but decided to visit the sanatorium first. I waited in the lobby from one to almost three a.m. "Gosh, I am sorry," said Pete, "Didn't mean to stay but a minute but I had to take a couple of drinks with him. Poor devil can't last till morning." "Then he would gallop all day to finish his rounds," said his nurse. To another patient it might be, "What the hell you laying around here for? Better get busy and find a job." One of Doctor Peters' "cures" told me, "I sent for Doctor Peters while I was suffering from fluid—wanted him to 'tap' me. Said Pete, 'You can stand it. It's good for you. You're getting on fine. Unless it gets unbearable, don't call me for a couple of months. Save your money!' "

LeRoy S. Peters was born April 5, 1882, in St. Joseph, Michigan, the only son of William F. and Eleanor Yund Peters, and was educated in public schools of his home town, the University of Minnesota and the Medical Department of the University of Illinois. Doctor Peters was most fortunate in his marriage to Isabella Fyfe on February 8, 1908. They have one child, Lawrence Fyfe Peters. Doctor Peters' first love in the medical field was diseases of the chest, in which he had planned to specialize before he developed tuberculosis in his final year at medical school. In 1906 he went to Silver City, New Mexico to regain his health and soon became Assistant Medical Director of the Cottage Tubercular Sanatorium, Silver City, under Dr. Earle S. Bullock. In 1913 he moved to Albuquerque as an associate of Dr. A. S. Shortle, in the management of the Albuquerque Sanatorium. From 1917 to 1926 he was Medical Director of St. Joseph Sanatorium, Albuquerque, after which he entered private practice, specializing in diseases of the chest. Doctor Peters pioneered in the Southwest in several forms of chest therapy, pneumothorax, pneumonolysis and thoracoplasty. His pioneering soul could never be content with anything as "right" merely because of its antiquity. As he matured professionally, he developed an increasing interest in social problems. He had concluded that poverty and tuberculosis walked hand in hand, that the well-to-do receiving proper care recovered from tuberculosis in almost any climate, while the poverty stricken patient with inadequate care could recover but little better in the Southwest than at home. He early became President of the Albuquerque Chamber of Commerce in the hope of finding sources of income for the large numbers of impoverished health-seekers constantly coming to the Southwest for its fabled cures. His enthusiastic championship of the underprivileged brought him into

LeRoy S. Peters
1882–1941

many conflicts with the *status quo* school. Too little attention to preventing and removing the conditions that breed disease, perhaps too much business was creeping into the healing profession. The wide-spread opposition that confronted his proposals for socialized medicine led him to study socialism and a careful consideration of the new Russian ideas. As a result, along with many able papers on tuberculosis, Doctor Peters had worked out and advocated a State Medicine Plan for the United States. In broad outline, his plan guaranteed adequate medical care for every citizen by placing the full duty on the medical profession. The members of the medical profession became virtually an arm of the government, entirely free to select its own means and methods, answerable only for results. Government, of course, supplied the funds, the profession disbursed, eradicated its own misfits and quacks and, Doctor Peters believed, would get results.

He was a member of the American Medical Association, the Committee (of 430 physicians) for the Improvement of Medical Care, the National Tuberculosis Association, the American Association for Thoracic Surgery and Euthanasian Society; Governor for New Mexico of the College of Physicians, President of the American Sanatorium Association, 1933–1934, and of the Southwestern Medical Society, 1938. None of the obligations of these associations were neglected; his humblest patient obtained the best service the medical profession could render and his miscalled leisure hours were devoted to a wider and deeper knowledge of tuberculosis treatment and his vigorous advocacy of a practical state medicine plan—and all this with complete awareness of his own depleted vitality. Coronary thrombosis, December 17, 1941, untimely ended a career that had added lustre to an honored profession and promised much for its future greatness.

George C. Taylor

AMERICAN TRUDEAU SOCIETY

Report of the Committee on Coexistent Syphilis and Tuberculosis

Dr. Henry D. Chadwick, *Chairman*

Dr. H. I. Spector Dr. H. S. Willis Dr. G. C. Turner

The first meeting of the Committee on Coexistent Syphilis and Tuberculosis was held at the office of Doctor Vonderlehr of the United States Public Health Service on September 10, 1941, to discuss plans and procedures for the guidance of the joint committee. Besides the members of the Committee, the following were present: Miss Lida Usilton, Senior Statistician, Division of Venereal Diseases of the U.S.P.H.S.; and Dr. J. H. Watkins, Professor of Vital Statistics of Yale.

A plan was evolved that would require the detailed study of the records of a large number of sanatorium patients. The sanatoria selected would be located in different parts of the United States so that the patients studied would represent a fair cross-section of the population. The records would be abstracted by field-workers employed by the Division of Venereal Diseases of the U.S.P.H.S. on forms prepared by the Committee. In the preparation of these forms, the codes and instructions, Miss Usilton has rendered invaluable assistance.

A second meeting of the Committee was held at Doctor Vonderlehr's office on February 2, 1942. The plans outlined at the previous meeting were reviewed in the light of war conditions as they affected the institutions that were expected to participate in the study. The sanatoria were being depleted of their medical and laboratory personnel to such an extent that it was becoming difficult to carry on the routine work. The Committee decided, therefore, to postpone the comprehensive plan that involved the study of large numbers of patients in different sections of the country as being impractical at this time. It was felt, however, that certain phases of the problem could be developed in two or three of the larger institutions where much material was available for study and assistance could be obtained for its tabulation. In a much curtailed way, the Committee expected to continue to function in such ways as war times would permit.

Since that time, the physicians in charge of three of the largest sanatoria, whom we hoped would find it possible to participate, have decided that they cannot do so at this time because of the shortage of personnel.

The Committee, therefore, regrets to report that this study will have to be postponed until the war emergency is over.

Report of the Committee on Coöperation with the American Board of Internal Medicine

Dr. J. Burns Amberson, Jr., *Chairman*

Dr. Paul P. McCain Dr. Lewis J. Moorman

Dr. William H. Oatway, Jr.

During the past year, this Committee has carried on its activities in accordance with the plan prescribed by the *American Board of Internal Medicine*, which now recognizes the subspecialty of tuberculosis and grants certification to physicians who are already certified in internal medicine and who are able to qualify by examination or otherwise in the subspecialty. No applications for certification are received by our Committee, as these go directly to the American Board of Internal Medicine. Those who apply for certification in the subspecialty submit their applications on forms provided for the purpose. The American Board then completes preliminary data and usually requests the opinion of our Committee as to whether the candidate is qualified to be admitted to the examination in the subspecialty. Our relationships with the American Board have been cordial, and it is believed that we are performing a useful service in coöperating as outlined above.

The American College of Physicians Will Hold Its 1943 Session in Philadelphia April 13-16, 1943

The American College of Physicians has announced its 27th Annual Session to be held in Philadelphia, Pennsylvania, April 13 to 16, inclusive, 1943. Heretofore, the College has held a five-day Session, but in the interest of conserving time and expense of its members, the program will be condensed into four days, Tuesday through Friday. Dr. James E. Paullin, Atlanta, as President of the College, will have charge of the program of General Sessions and Lectures. Dr. George Morris Piersol, Philadelphia, as General Chairman, will be responsible for the program of Hospital Clinics, Panel Discussions, local arrangements, entertainment, etc. The general management of the session and technical exhibits will be handled by the Executive Secretary, Mr. E. R. Loveland, 4200 Pine St., Philadelphia.

Other medical societies are urged to avoid conflicting dates, for our mutual benefit.

THE ISOLATION AND IDENTIFICATION OF PATHOGENIC FUNGI FROM SPUTUM

By

JOSEPH M. KURUNG

From the New York State Hospital for Incipient Pulmonary Tuberculosis,
Ray Brook, New York

FOREWORD

Diseases of the lung due to infection by fungi have been regarded as extremely rare. Recent studies, however, have disclosed that such infections are not uncommon and that the pulmonary lesions encountered are as varied in nature as those in tuberculosis. The diagnosis usually is established by the recovery of the offending fungus from the sputum. Their identification may prove a formidable task to those not familiar with the subject. The terminology and classification is difficult to master and the morphology and cultural characteristics vary widely.

The manual presents the essential laboratory procedures and the conditions required for the optimal cultivation of the pathogenic fungi found in the sputum. The age of the culture and the magnification adopted for the microscopical study are exactly stated, an important feature. The appearance of the colony and the microscopical details are liberally illustrated. It would seem that the information contained in the manual should suffice for the identification of the offending fungus in the sputum.

HARRY A. BRAY
Ray Brook, New York

COLLECTION OF THE SPUTUM

The collection of the sputum is an important feature. The specimen should be obtained by the physician or some other qualified person. It should be collected in the morning, preferably before breakfast. The patient is instructed, first to brush the teeth, rinse the mouth and gargle the throat with a mouth wash. Great care must be exercised to see that the sputum comes from the lungs. Avoid all specimens of saliva or nasopharyngeal secretions. Sterilized petri dishes serve best for the collection of the sputum, which should be immediately sent to the laboratory to avoid contamination, and the growth of any bacteria present in the sputum.

Carefully examine the sputum, best with a hand lens, for the presence of tiny particles or flecks, one-half to three millimeters in diameter, yellowish or gray in color and that appear denser than the surrounding sputum. The flecks, when present, often contain fungi in large numbers and should be selected for the microscopical study and the inoculation of the medium.

PREPARATION OF THE SPUTUM FOR MICROSCOPICAL STUDY

Tease off a small specimen of sputum with a pair of toothpicks or a loop. Place on a clean glass slide, add one or two drops of 10 per cent sodium hydroxide and mix thoroughly. Place a cover glass over the preparation and allow it to stand three to five minutes. Examine preparation with low and high, dry lens in a subdued light. If no fungi are found by this method, concentrate the sputum. Put the sputum in a 50 cc. centrifuge tube; add approximately twice the amount of 4 per cent sodium hydroxide. Place the tube in boiling water for approximately five minutes, stirring the contents occasionally with a glass rod. Centrifuge for twenty minutes at high speed, decant the supernatant fluid and resuspend the sediment in 2 cc. of distilled water. Put one loopful of the mixture on a clean glass slide and place a cover glass over the preparation.[1] The microscopical study of the unstained preparation of the sputum permits one to identify some of the pathogenic fungi found in the sputum. However, it is advisable in each instance to confirm the microscopical observation by cultural studies.

PREPARATION OF MEDIA FOR THE CULTIVATION OF FUNGI

Sabouraud's agar medium is the standard medium for the isolation of fungi, and is prepared as follows:

Dextrose	40.0 g.
Peptone	10.0 g.
Agar	20.0 g.
Distilled water	1000.0 cc.

Heat over steam bath or in autoclave until the ingredients are completely dissolved. Adjust the medium to a pH 5.2 to 5.5 by the addition of normal hydro-

[1] The concentration of the sputum kills the fungus and the material, therefore, should not be used for the inoculation of the medium.

chloric acid. Dispense the medium in lots of 50 to 100 cc. in glass bottles; sterilize in autoclave for fifteen minutes at 15 pounds pressure. Place the medium in the refrigerator for future use. The medium preparatory to use is melted in a steam bath or autoclave, poured into petri dishes and allowed to solidify, preparatory to inoculation.

Dextrose Yeast Extract Medium

Dextrose	8.0 g.
Sodium chloride	1.7 g.
Yeast extract, Difco	0.5 g.
Distilled water to make	200 cc.

Adjust the undiluted medium to pH 4 with normal hydrochloric acid.

The medium is dispensed in test tubes in lots of 5 cc. and sterilized in the autoclave for fifteen minutes at 15 pounds pressure. The medium is ready for use on cooling.

Certain pathogenic fungi found in the sputum, *Actinomyces*, *Blastomyces* and *Histoplasm capsulatum*, require dextrose blood agar medium at a pH of 7.2 for their initial cultivation. The medium consists of nutrient agar with the later addition of dextrose and fresh blood.

Nutrient Agar

Meat extract	3 g.
Peptone	10 g.
Sodium chloride	5 g.
Agar	25 g.
Distilled water	1000 cc.

Dissolve ingredients by heating in steam bath or autoclave. Adjust the medium to pH 7.4. Dispense in 100 cc. lots and sterilize by autoclaving for fifteen minutes at 15 pounds pressure. The final reaction should be pH 7.2.

Dextrose Blood Agar

Nutrient agar	100 cc.
Blood	5–10 cc.
Dextrose, 20 per cent solution	5 cc.

The agar base is melted and then cooled to 45°C. The sterile dextrose solution and blood are added, the contents gently mixed and poured into petri dishes. After solidification, and following the inoculation with sputum, the plates are incubated under aerobic and anaerobic conditions at a temperature of 37° C. The colonies may first appear only after a lapse of two or three weeks.

Sabouraud's medium, excellent for the cultivation of fungi, has the objection that it permits the growth of many bacteria commonly found in the sputum, and one or more transplants may be required before the fungus is isolated in pure culture. Dextrose yeast extract medium is easily prepared and is comparable

to Sabouraud's for the cultivation of fungi and, with a pH of 4, effectively prevents the growth of all organisms in the sputum except the fungus. The initial inoculation, therefore, is made on dextrose yeast extract medium. The tubes are incubated at a temperature of 37° C. and inspected daily for seven days. If a growth is obtained, the culture should be transplanted to Sabouraud's medium to observe the development and appearance of the colonies. If no growth occurs in dextrose yeast extract medium, a specimen of fresh sputum should be inoculated on glucose blood agar and cultivated under aerobic and anaerobic conditions at a temperature of 37° C. In some instances three weeks may elapse before the first colonies appear.

SLIDE CULTURE METHOD

This permits one to witness the manner in which the fungus develops and multiplies, and is an aid in the identification of the fungus. A few cubic centimeters of melted Sabouraud's agar are poured on a clean 2 x 3 inch glass slide, allowed to solidify and the surface inoculated with a loopful of sputum, or preferably with a culture grown in dextrose yeast extract. A clean, No. 1, cover glass, somewhat smaller than the glass slide, is placed over the surface of the media. The cover glass is rimmed with vaseline, allowing a small opening at one end for the entrance of air, and incubated at 37° C. The prepared glass slide should be kept moist by placing it in a petri dish lined with a thin layer of moist cotton.

THE IDENTIFICATION OF THE FUNGUS

The distribution of the growth, and the size, shape and color of the colonies should be noted. Observe the outline of the colony and whether the surface is smooth and nonfilamentous, or rough and filamentous.

Microscopical examination of the colony: There are accompanying illustrations of the component parts of the fungus and their designated terms. Prepare an unstained slide preparation of the colony as described above. There is no advantage to stained preparations with the exception of the *Actinomyces*, and here a Gram stain should be used and the preparation examined with the oil immersion lens because of the minute size of the organism. Otherwise, look for yeast-like budding cells and mycelia, which may be septate or nonseptate, or of the racquet form. Note the presence or absence of the sporeheads, arthrospores and chlamydospores. The identification of the fungus is based on the appearance of the mycelium, together with the location, the numbers, size and appearance of the spores. The accompanying descriptions and illustrations will be found helpful in the identification of pathogenic fungi. It is important to bear in mind, in making the comparisons, that the colony should conform to the age stated in the text for the illustrations. In some instances, the size and appearance of the colony may vary widely with its age. In making a microscopical comparison, the same magnification should be used as stated in the text.

The recovery and identification of the pathogenic fungus should be confirmed on several occasions, a safe and excellent rule in mycotic diseases of the lungs.

REFERENCES

(1) Henrici, Arthur T.: Molds, Yeasts and Actinomycetes, John Wiley & Co., New York.
(2) Dodge, Carroll W.: Medical Mycology, The C. V. Mosby Co., St. Louis, Mo.
(3) Jacobson, Harry P.: Fungus Diseases, Charles C. Thomas, Springfield, Ill.
(4) Lewis, George M., and Hopper, Mary E.: An Introduction to Medical Mycology, The Year Book Publishers, Inc., Chicago, Ill.
(5) Castellani, Aldo: Fungi and Fungus Diseases, American Medical Association, Chicago, Ill.
(6) Thom, C., and Church, M.: The Aspergilli, Williams & Wilkins Co., Baltimore, Md.

Plate I

ILLUSTRATIONS OF THE IMPORTANT MORPHOLOGICAL TERMS USED IN MYCOLOGY

Fig. 1. Thallus—or colony.
Fig. 2. Hyphae—one of the filaments.
Fig. 3. Mycelia—a collection of hyphae, the vegetative body of a fungus.
Fig. 4. Mycelia, septate.
Fig. 5. Mycelia, Non-septate.
Fig. 6. Sporehead (Aspergillus).
a. conidiophore.
b. vesicle.
c. conidia.

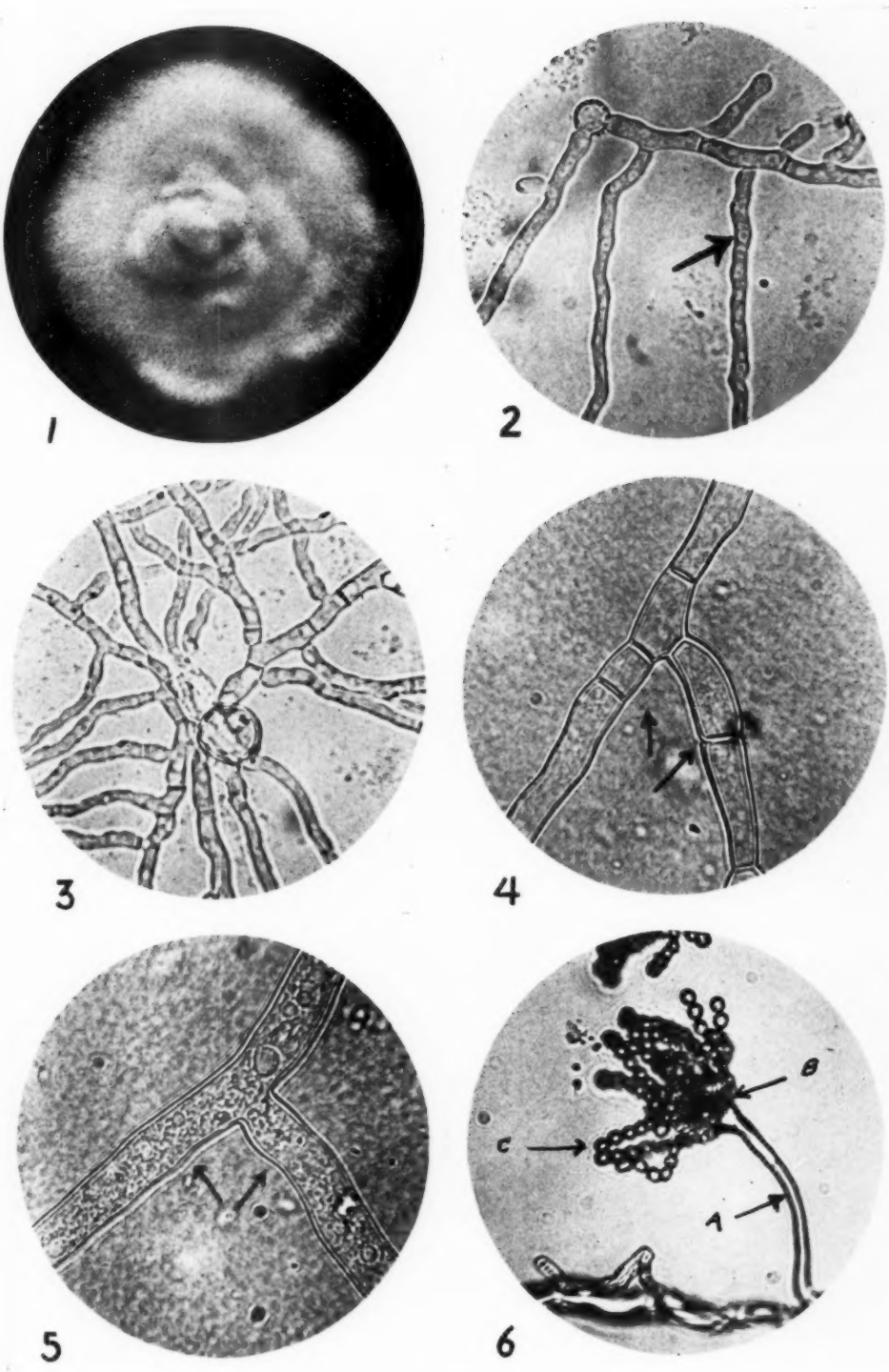


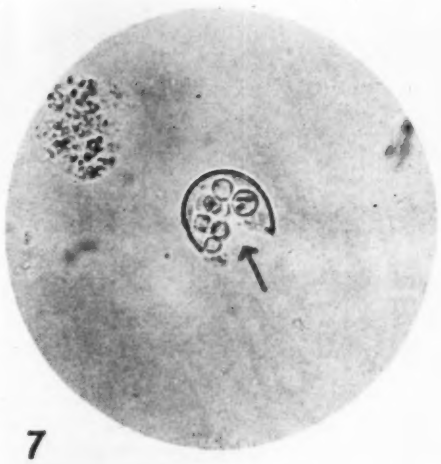
PLATE I

PLATE II

ILLUSTRATIONS OF THE IMPORTANT MORPHOLOGICAL TERMS USED IN MYCOLOGY

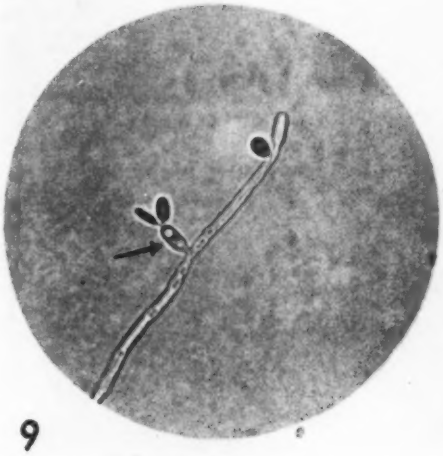
FIG. 7. Endospores.
FIG. 8. Blastospore or budding form.
FIG. 9. Sporophore.
FIG. 10. Arthrospores.
FIG. 11. Ascospores.
FIG. 12. Chlamydospore.

Definitions of these terms can be found in the standard reference books listed at the end of this article.

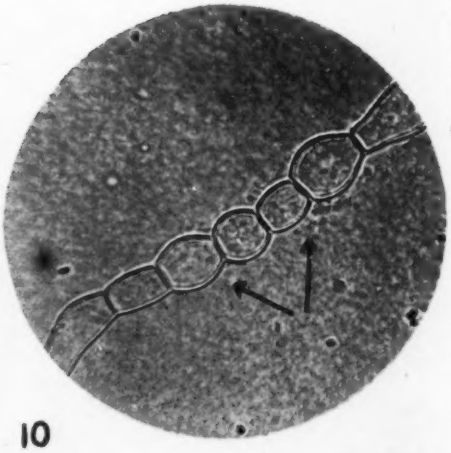


7

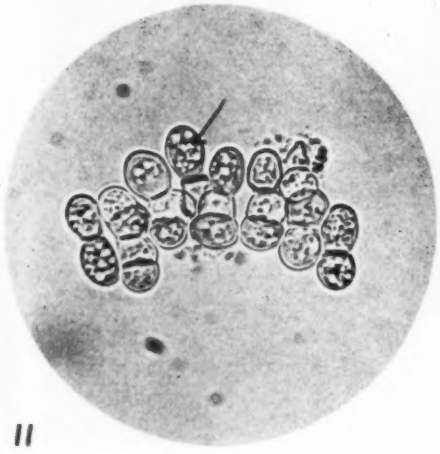
8



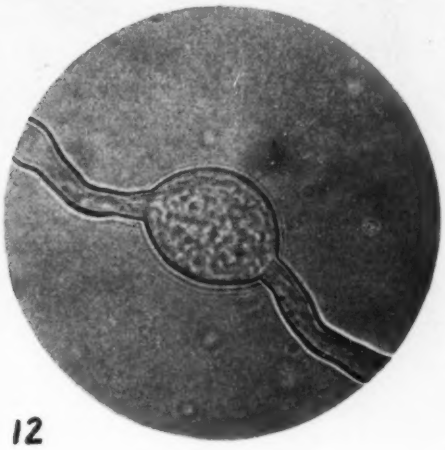
9



10



11



12

PLATE II

PLATE III

MONILIA ALBICANS

On microscopical examination of the fresh sputum, the microörganisms are seen as round or oval, and occasionally elongated cells, 2 to 5 μ in diameter, singly or in pairs, or in small clusters. Budding forms and short strands of mycelium, at times branched, may be present. A small nucleus within the cell is frequently seen (figure 1).

Artificial Media: Growth appears within twenty-four to forty-eight hours. On Sabouraud's agar medium the colonies (figure 2) are round, smooth and elevated. The color may be white, gray or cream. The colonies may develop a coarse or fine mycelial fringe which penetrates into the medium (figure 3). The surface may become coarsely lobulated and may develop numerous small folds over the central portion. The colonies have a pasty consistency and a strong yeast-like odor. On dextrose yeast extract medium the solution becomes cloudy and a heavy flocculent deposit with a pasty ring and bubbly surface may form. In other cases, the medium may become cloudy with a fine layer of cells at the bottom of the tube.

Microscopically, the organisms are seen as round or oval cells, varying in size from 3 to 9 μ in diameter with numerous budding forms present (figure 4). Occasional elongated cells connected to one or more round or oval cells are seen (figures 5 and 6). Large vacuoles and granules within the cells are often present.

FIG. 1. Unstained slide preparation of sputum showing *Monilia albicans*. × 800.

FIG. 2. Colonies of *Monilia albicans* grown on Sabouraud's agar, four days at 37° C. Actual size.

FIG. 3. Two colonies, magnified, showing a smooth and a mycelial type of colony. Grown on Sabouraud's agar, four days at 37°C. × 8.

FIG. 4. Unstained slide preparation made from colony grown on Sabouraud's agar for four days at 37° C. × 800.

FIG. 5. Unstained slide preparation made from culture grown in dextrose-yeast extract medium, four days at 37° C. × 800.

FIG. 6. Slide culture grown on Sabouraud's agar four days at 37° C. × 800.

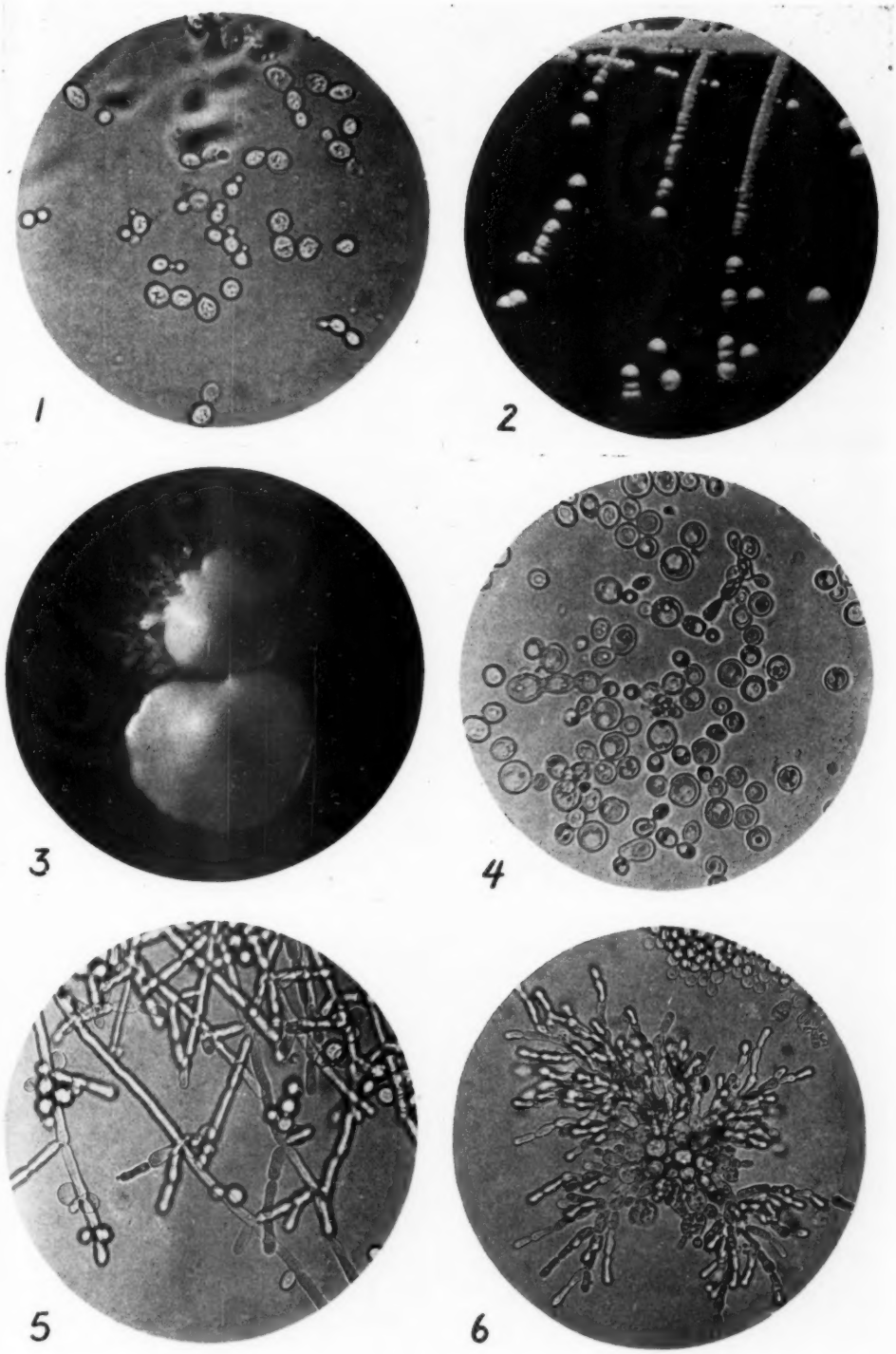


PLATE III

PLATE IV

CRYPTOCOCCUS

On microscopical examination of the fresh sputum the microörganisms appear as spherical cells, with a thick-walled capsule ranging in size from 5 to 15 μ diameter. The protoplasm may contain one or more refractile granules and vacuoles. Budding forms are always present. Mycelial forms are absent.

Artificial Media: Growth appears within forty-eight to seventy-two hours. On Sabouraud's agar medium, the colonies appear round, smooth, shiny and cream-white in color (figures 1 and 2). They become confluent and yellowish with age. No mycelium ever develops. In dextrose yeast extract medium, growth forms a slight turbidity with a fine sediment. Pellicle and pasty ring on surface are absent.

Microscopically, the microörganisms are seen as spherical cells with well developed capsules, 5 to 10 μ in diameter (figures 3, 4, 5 and 6). The protoplasm is finely granular and the larger cells may contain one or more vacuoles. Budding forms are always present.

FIG. 1. Colonies of *Cryptococcus* grown on Sabouraud's agar, five days at 37° C. Actual size.

FIG. 2. *Cryptococcus* colony grown on Sabouraud's agar, five days at 37° C. magnified. × 6.

FIG. 3. Unstained slide preparation made from colony grown on Sabouraud's agar, five days at 37° C. × 400.

FIG. 4. Same as figure 3. × 800.

FIG. 5. Unstained slide preparation made from dextrose-yeast extract culture, five days at 37° C. × 800.

FIG. 6. Slide culture, grown on Sabouraud's agar, five days at 37° C. × 800.

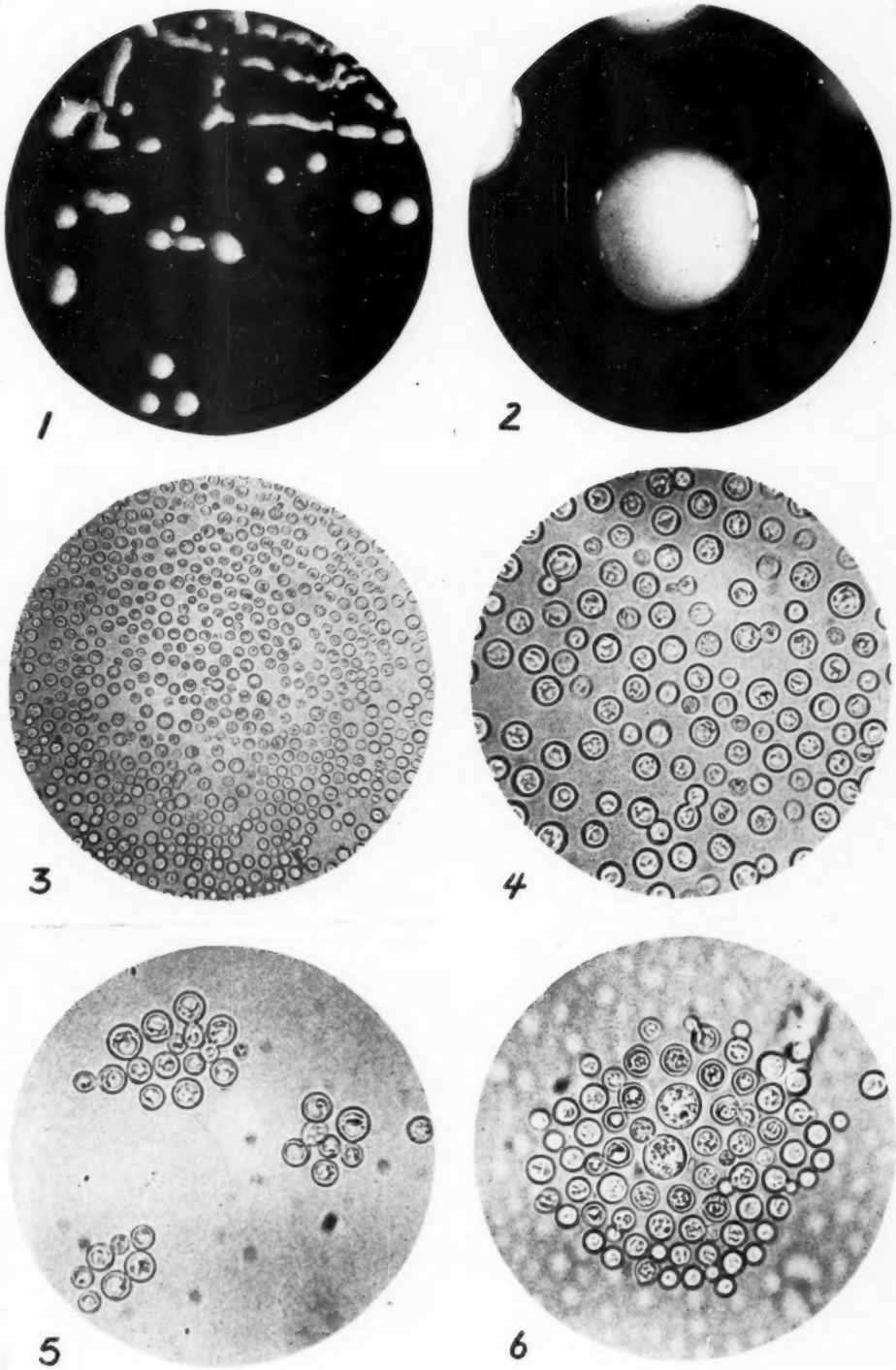


PLATE IV

PLATE V

COCCIDIOIDES IMMITIS

On microscopical examination of the fresh sputum the microörganisms appear as round, doubly-contoured spherules, varying from 5 to 70 μ in diameter (figure 1). They may be seen in different stages of development. The young cells have a thin wall and contain finely granular protoplasm (figure 1A) while the older cells have a thicker wall and contain large numbers of small round endospores (figures 1b and C). Other cells appear as mere shells (figure 1D), only the wall remaining, at times with a few scattered spores near the ruptured cell.

Artificial Media: Growth appears in two to ten days. On Sabouraud's agar medium the colonies appear as small, white, fuzzy plaques (figures 2 and 3), gradually becoming larger and covered with an abundance of white, aerial hyphae. The color changes to brown with age. Microscopically, there is an abundance of branching, septate mycelium, with hyphae 2 to 4 μ in diameter, and giving rise to racquet mycelium (figure 4A) and chlamydospores, 4 to 10 μ, and arthro-spores 3 to 6 μ in diameter (figure 4B).

In dextrose-yeast extract medium, the colonies appear as small, white, fluffy snow-flake-like colonies at the bottom of the tube, the medium remaining clear. Microscopically, each colony appears as a mass of tangled, branching septate mycelium with an abundance of chlamydospores (figure 5A) and arthrospores (figure 5B).

FIG. 1. *Coccidioides immitis* spores in sputum. × 800.

FIG. 2. *Coccidioides immitis* colonies on Sabouraud's agar, seven days at 37° C. Actual size.

FIG. 3. *Coccidioides immitis*, colony grown on Sabouraud's agar, seven days at 37° C. magnified. × 6.

FIG. 4. Unstained slide preparation made from colony grown on Sabouraud's agar, seven days at 37° C. × 800.

FIG. 5. Unstained slide preparation made from culture grown in dextrose-yeast extract medium, seven days at 37° C. × 800.

FIG. 6. Slide culture of *Coccidioides immitis*, grown on Sabouraud's agar, seven days at 37° C. × 800.

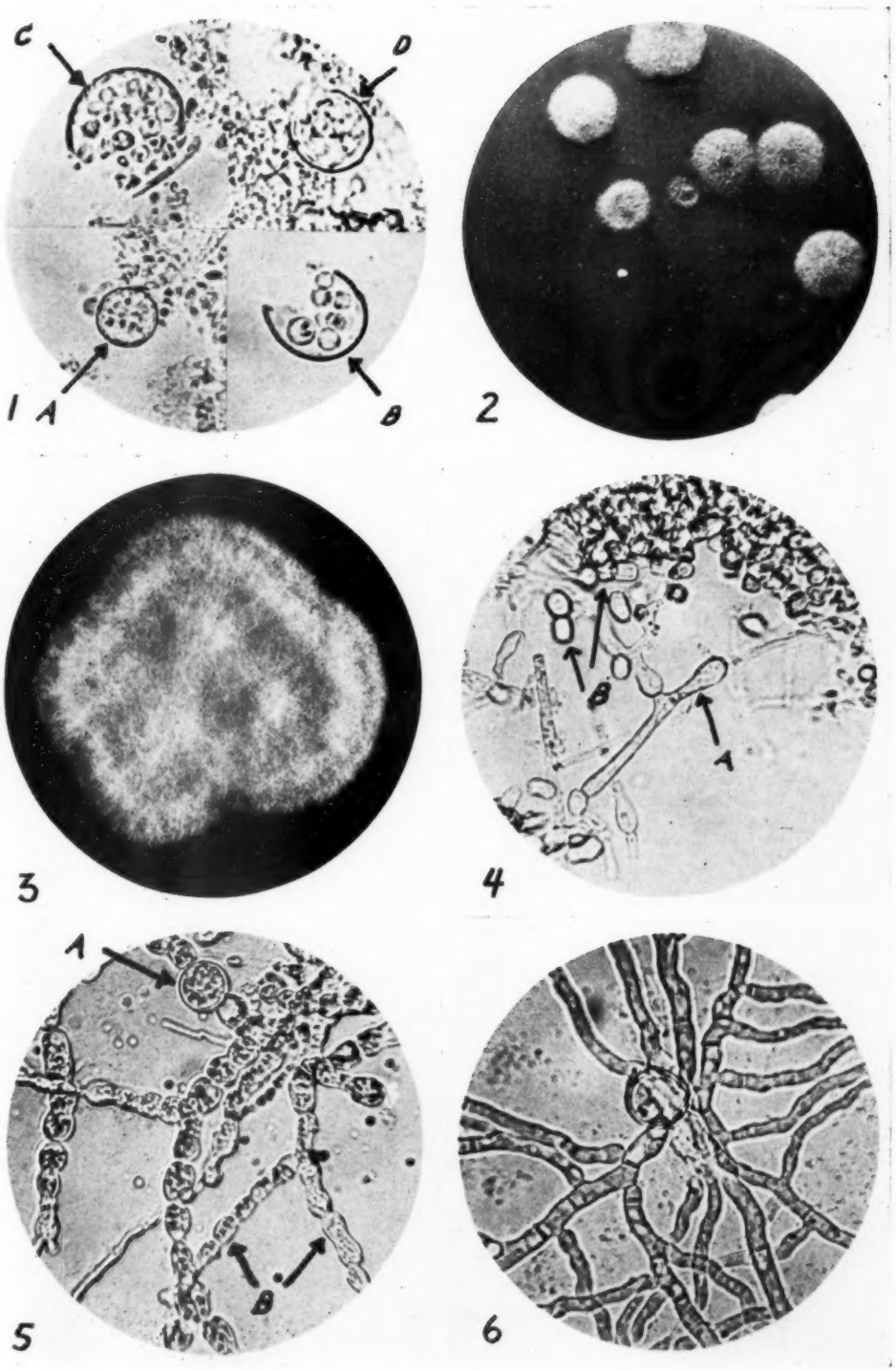


PLATE V

PLATE VI

BLASTOMYCES

On microscopical examination of the fresh sputum the microörganisms appear as round or oval cells 10 to 15 μ in diameter, having a well-marked, highly-refractile, double-contoured capsule; they are found singly or in small clusters (figure 1). The protoplasm is granular and may contain one or more refractile vacuoles (figure 1A). Budding forms are always seen (figures 1B and C). No mycelium occurs in pus.

Artificial Media: Both dextrose blood agar and Sabouraud's agar media should be used. Colonies appear in three to seven days or later. On dextrose blood agar at 37° C. the colonies are yellowish brown in color, wrinkled and similar to those of tubercle bacilli (figure 2). They are friable and easily broken into small fragments on the slide. Aerial hyphae are not present. Microscopically, one observes round or oval budding forms, similar to those found in sputum or pus. The cell wall is thick and highly refractile (figure 5).

On Sabouraud's medium the organisms appear as small white fuzzy colonies which gradually increase in size and become covered with fine, white, aerial hyphae (figure 4). Colonies usually become brown with age. Microscopically these are branching, septate, mycelium with cells 3 to 4 μ in diameter. Older cultures develop racquet mycelium with cells 5 to 6 μ at the swollen end, tapering to 2 to 4 μ and in addition terminal or lateral conidia 6 to 8 μ in diameter are present (figure 6).

In liquid media, such as meat-infusion broth, the organisms grow as tufted masses in the bottom of the tubes, the medium remaining clear. As the culture becomes older, a white fluffy pellicle is formed. Microscopically these organisms are similar to those grown on Sabouraud's medium.

FIG. 1. Blastomyces spores in pus. × 800.

FIG. 2. Dry, wrinkled type of colony grown on dextrose blood agar, twelve days at 37° C. magnified. × 6.

FIG. 3. Wooly type of colony grown on Sabouraud's agar, twelve days at 37° C. Actual size.

FIG. 4. Wooly type of colony grown on Sabouraud's agar, twelve days at 37° C. magnified. × 6.

FIG. 5. Unstained slide preparation made from colony grown on dextrose blood agar, twelve days at 37° C. × 800.

FIG. 6. Unstained slide preparation made from culture on Sabouraud's agar, twelve days at 37° C. × 800.

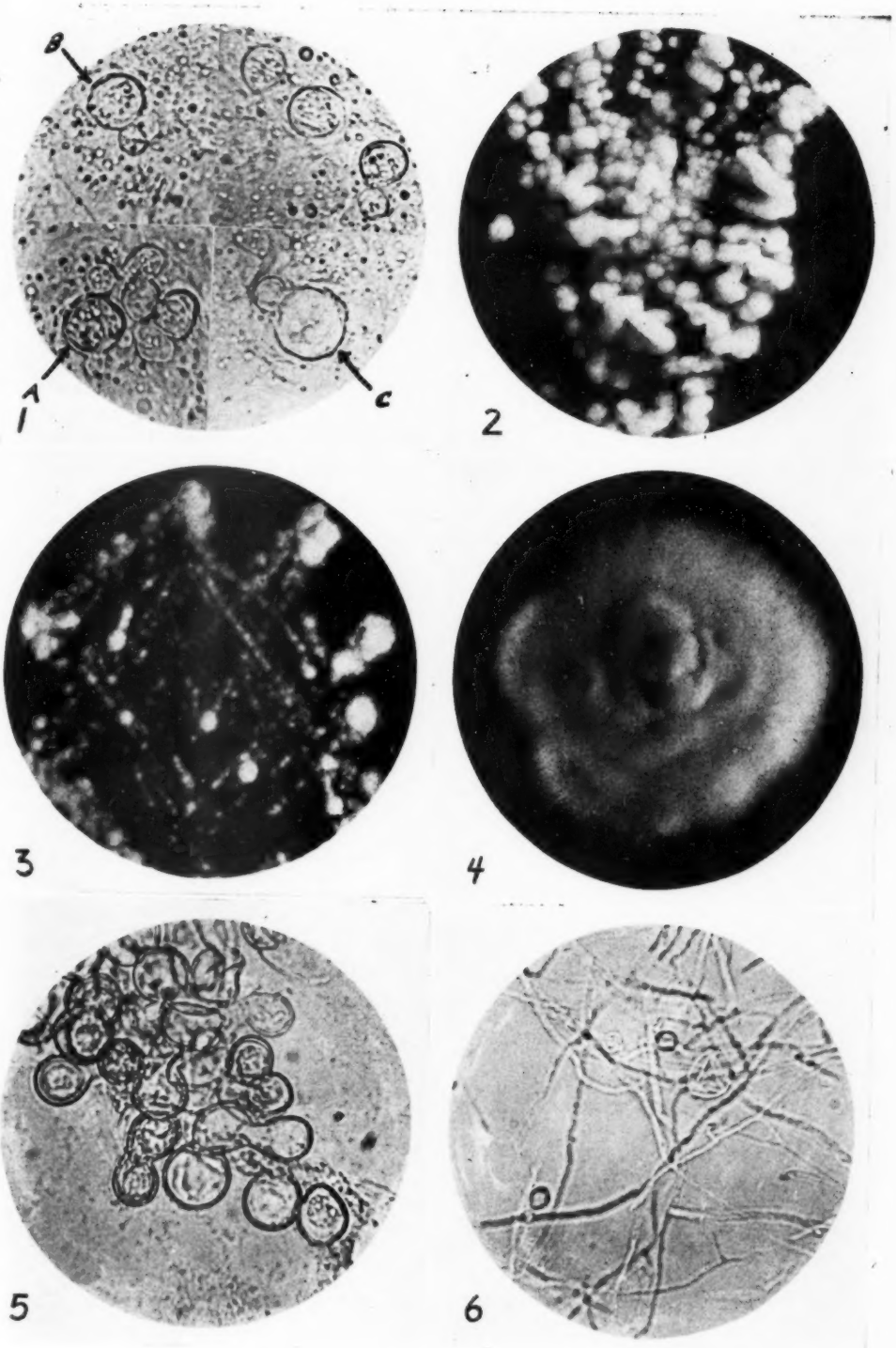


PLATE VI

PLATE VII

SPOROTRICHUM

On microscopical examination of the fresh sputum the microörganisms are seen as oval or cigar-shaped bodies from 2 to 4 μ in length and from 1 to 3 μ in width, found singly or in small clusters. They are frequently seen within pus cells. The protoplasm is finely granular and the cell surrounded by a thin capsule. The organisms resemble short, thick bacilli.

Artificial Media: Growth appears in three to ten days. On Sabouraud's agar medium, white, pin-head sized colonies which soon become surrounded by a finely-rayed fringe are seen (figures 1 and 2). Later the colonies increase in size, become convoluted, wrinkled and penetrate the medium. They may coalesce. Older cultures become brown to black. In dextrose yeast extract medium, growth develops slowly as small, white fluffy colonies at the bottom of the tube; the liquid remaining clear. The colonies gradually become larger and form a thick membrane on the surface.

Microscopically these microörganisms are seen as branching, septate mycelium about 2 μ in diameter (figure 3A). The spores, 3 to 5 μ in diameter, are single or grouped, and develop along the length of the filaments, usually terminating them (figures 5A and B). Classification is based chiefly on the size, shape and position of the conidia (figures 3, 4, 5 and 6).

FIG. 1. *Sporotrichum* colonies grown on Sabouraud's agar, five days at 37° C. Actual size.

FIG. 2. Colony grown on Sabouraud's agar, five days at 37° C. magnified. × 4.

FIGS. 3 and 4. Unstained slide preparation made from colony grown on Sabouraud's agar, five days at 37° C. × 800.

FIG. 5. Unstained slide preparation made from culture grown in dextrose yeast extract medium, five days at 37° C. × 800.

FIG. 6. Slide culture, grown on Sabouraud's agar, five days at 37° C. × 800.

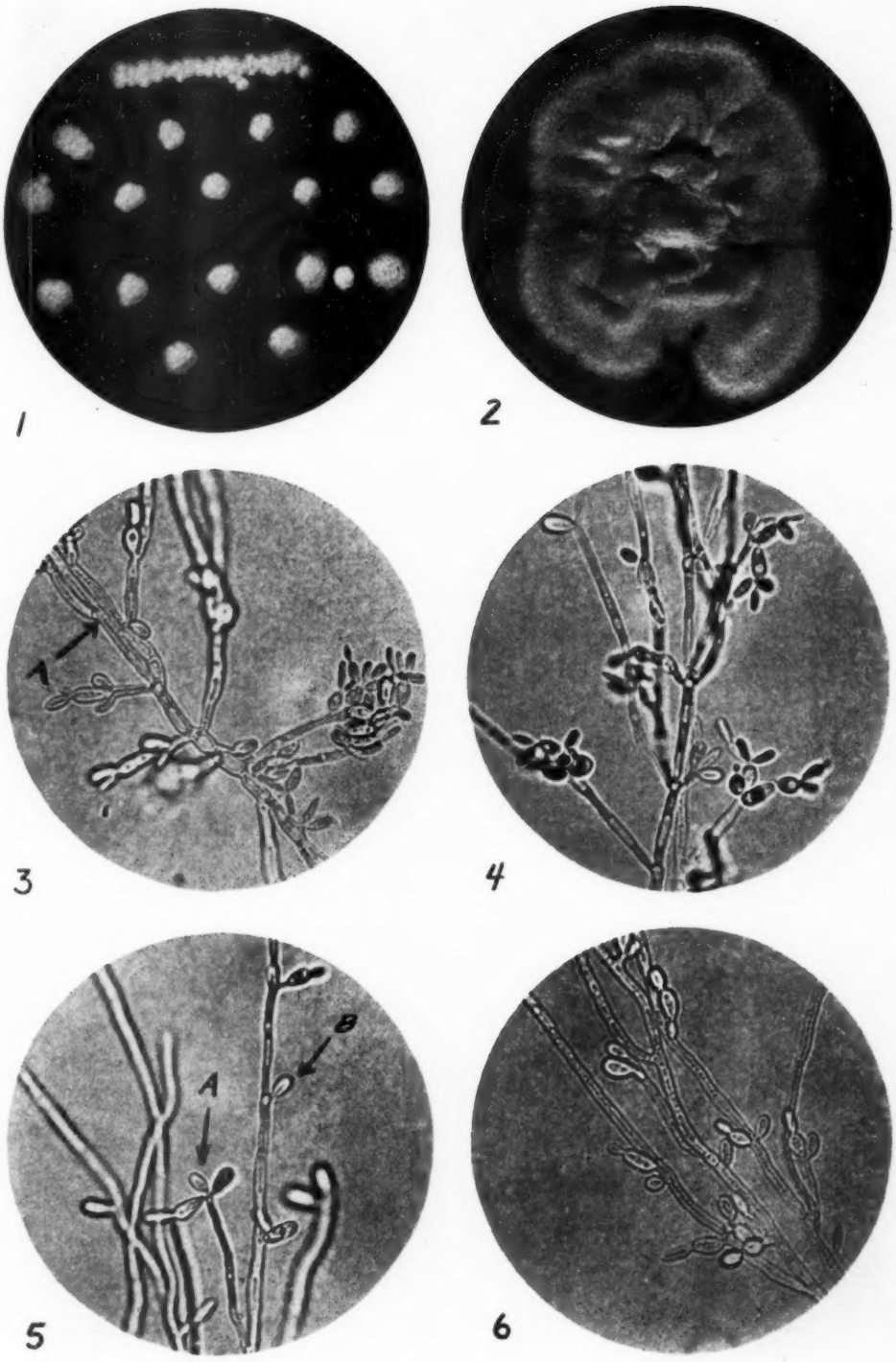


PLATE VII

PLATE VIII

ASPERGILLUS

On microscopical examination of fresh sputum these microörganisms are seen as round or slightly oval bodies 2 to 3 μ in diameter, and occasionally as branching septate mycelial filaments.

Artificial Media: Growth appears within twenty-four to forty-eight hours. On Sabouraud's agar medium, the colonies are small, white and fuzzy (figures 1 and 2). These rapidly increase in size and soon coalesce to form large colonies. The color of growth, which may be green, yellow, brown or black, varies with the particular species cultures. *Aspergillus fumigatus* is the species most commonly isolated from cases resembling pulmonary tuberculosis. This species has a dark green velvety appearance on culture media. It is important to point out at this time that many saprophytic species of aspergilli are—along with the *Mucor* and *Penicillia*—the most common laboratory contaminants to be encountered in this type of work. Differential description of the many species of aspergilli can be found in the book *The Aspergilli* by Thom and Church. In dextrose yeast extract medium, the organisms develop in the bottom of the tube as a small filamentous mass. This gradually increases in size until growth appears on the surface of the medium forming the characterisic growth of aspergilli.

Microscopically these microörganisms appear as branching, septate mycelium 2 to 5 μ in diameter (figures 3 and 4). Conidiophores (figure 3A), which arise from large and prominent foot cells, along the mycelium, terminate in a swollen portion called the vesicle (figure 3B). From the latter there are given off a number of small stalks or sterigmata which in turn bear the chain of rounded conidia (figure 3C). The arrangement of these component parts presents a compact mass of spores and these elements together serve as an aid in identifying the fungus.

FIG. 1. Colonies of *Aspergillus* grown on Sabouraud's agar, forty-eight hours at 37° C. Actual size.

FIG. 2. *Aspergillus* colony, grown on Sabouraud's agar, forty-eight hours at 37° C. magnified. × 3.

FIG. 3. Unstained slide preparation of *Aspergillus* grown on Sabouraud's agar, forty-eight hours at 37° C. Note the spore head in the centre of the field, surrounded by conidia and mycelial filaments. × 400.

FIG. 4. Same as figure 3. × 800.

FIG. 5. Unstained slide preparation made from culture grown in dextrose yeast extract medium forty-eight hours at 37° C. × 800.

FIG. 6. Slide culture of *Aspergillus*, grown on Sabouraud's agar, four days at 37° C. × 800.

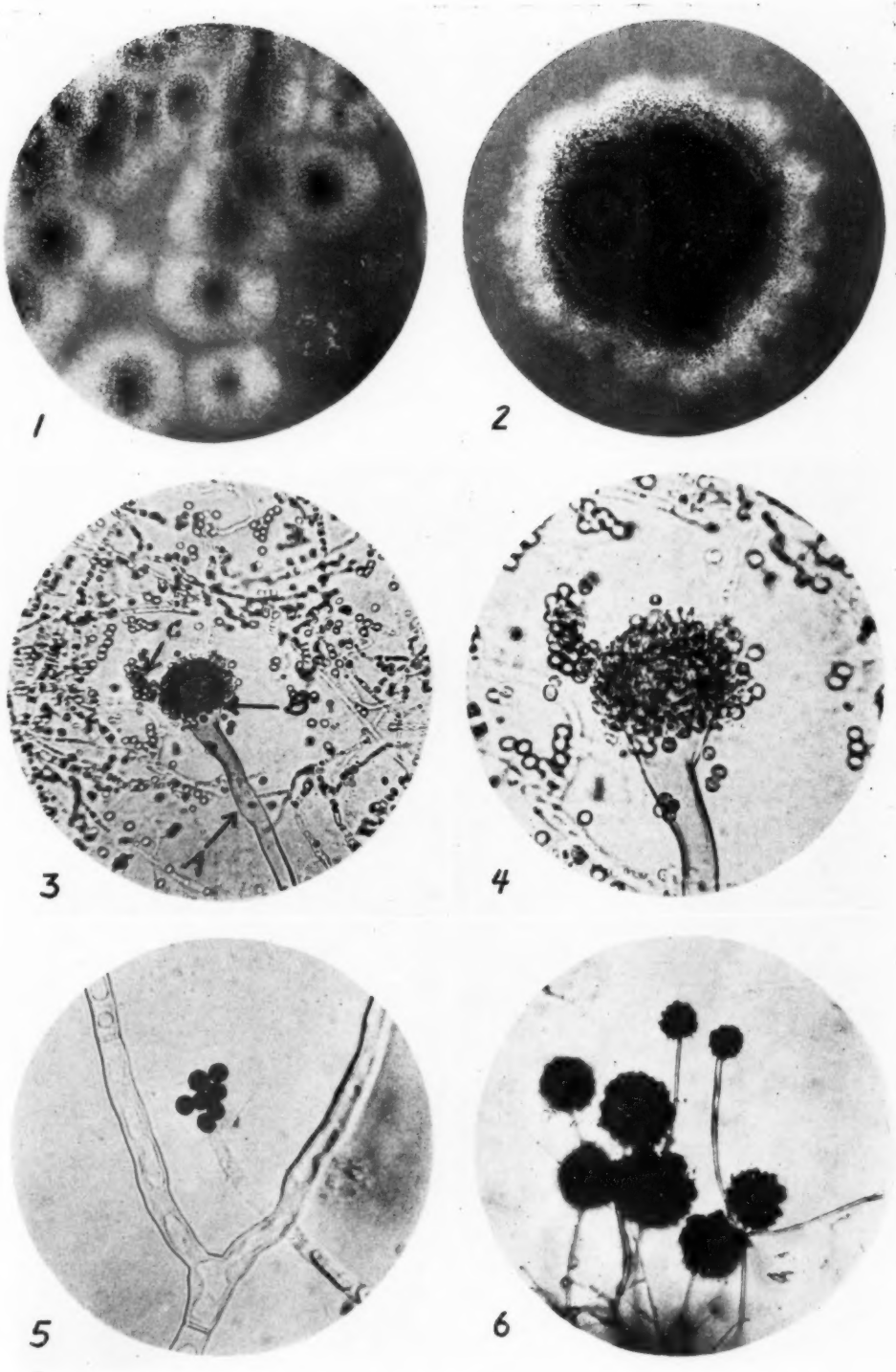


PLATE VIII

PLATE IX

GEOTRICHUM

On microscopical examination of the fresh sputum the microörganisms are seen as spherical cells 4 to 5 μ in diameter, with a thin, double-contoured membrane. The protoplasm is finely granular and may contain a few large vacuoles. Budding forms are absent.

Artificial Media: Growth appears within twenty-four to forty-eight hours. On Sabouraud's agar medium the colonies are small, white and fuzzy (figures 1 and 2). They rapidly increase in size and have a characteristic radiating appearance. These colonies are membranous and adherent to the medium. Color is white; older cultures may become yellow to amber. Dextrose yeast extract medium becomes cloudy. Pellicle and heavy flocculent deposits are formed. Older cultures show a thick filamentous growth on the surface.

Microscopically the microörganisms exhibit septate mycelium 3 to 7 μ in diameter, the cell of which become elongated and separate into chains of arthrospores which are spherical, ellipsoid or cylindrical in appearance, and vary in size from 4 to 9 μ in diameter, and 5 to 20 μ in length (figures 3, 4 and 5).

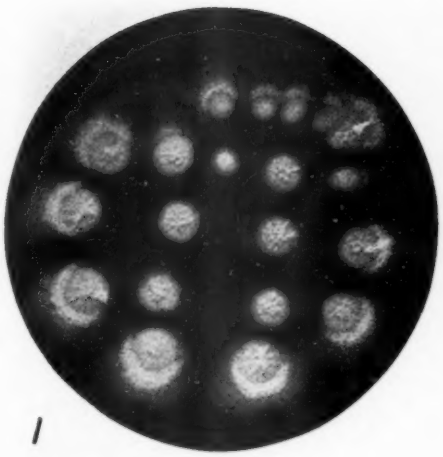
FIG. 1. *Geotrichum* colonies grown on Sabouraud's agar, four days at 37° C. Actual size.

FIG. 2. *Geotrichum* colonies on Sabouraud's agar, four days at 37° C. magnified. × 2.

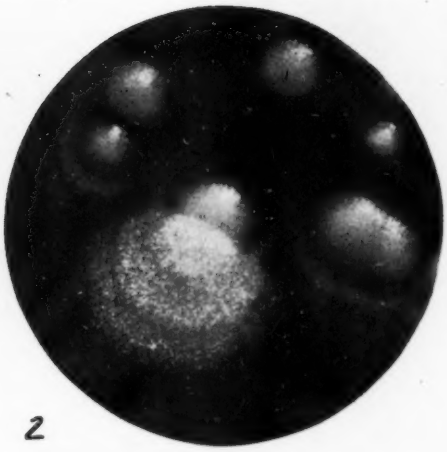
FIGS. 3 and 4. Unstained slide preparation made from colony grown on Sabouraud's agar, four days at 37° C. × 800.

FIG. 5. Unstained slide preparation made from culture grown in dextrose yeast extract medium, four days at 37° C. × 800.

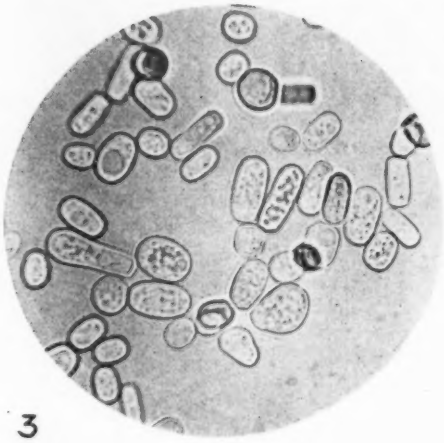
FIG. 6. Slide culture grown on Sabouraud's agar, four days at 37° C. × 800.



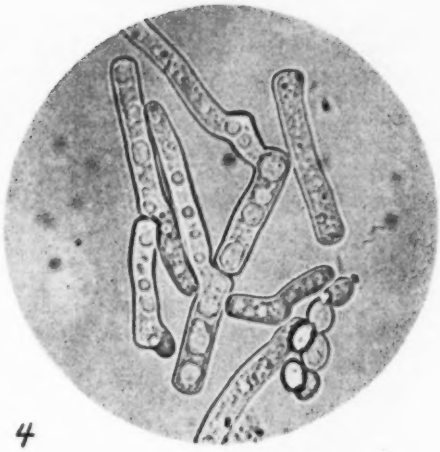
1



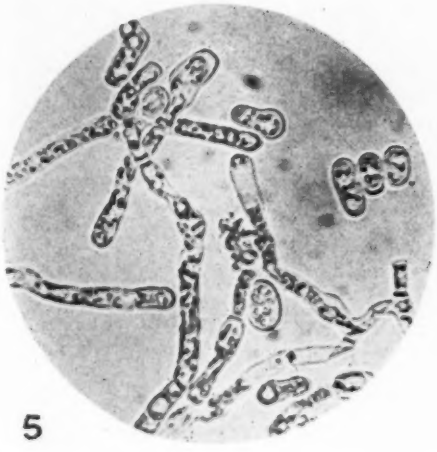
2



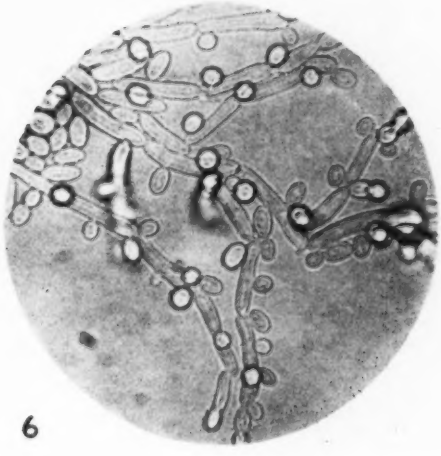
3



4



5



6

PLATE IX

PLATE X

HISTOPLASMA CAPSULATUM

On microscopical examination of the fresh sputum the microörganisms appear as round or oval yeast-like cells, usually with one budding cell attached, measuring 2 to 4 μ in diameter and surrounded by a thin, well defined refractile capsule. A large vacuole and a granule are frequently present within the cytoplasm.

Artificia Media: There are two different forms of this fungus, the yeast-like form as seen in pus and tissue and when grown on dextrose blood agar, and the mycelial form which is seen when grown on Sabouraud's agar medium.

Growth is slow, usually requiring four to ten days at 37° C. before the colonies become visible. On Sabouraud's agar medium, the colonies are white and cottony, slowly increasing in size while the aerial hyphae become more abundant (figures 1 and 2). Older cultures change from white to a light brown color. Microscopically, this microörganism gives rise to septate, branching mycelia, 2–4 μ in diameter. Along the hyphae, and usually terminating short lateral branches, can be seen round or pyriform spores, 3 to 10 μ in diameter. The characteristic identifying structures are the large, thick-walled, round or pyriform tuberculated chlamydospore, varying in size from 7 to 20 μ in diameter (figures 3 and 4).

On dextrose blood agar, the growth appears as small pasty colonies. Microscopical preparations made from these colonies exhibit small, round or oval yeast like cells, 2 to 4 μ in diameter, similar to those found in sputum. Budding forms are present and a large granule and vacuole may be seen within the cell.

FIG. 1. Colonies of *Histoplasma capsulatum* grown on Sabouraud's agar, nineteen days at 37° C. Actual size.

FIG. 2. Colonies of *Histoplasma capsulatum* grown on Sabouraud's agar, nineteen days at 37° C. magnified. × 6.

FIG. 3. Unstained slide preparation made from colony grown on Sabouraud's agar, nineteen days at 37° C. × 400.

FIG. 4. Same as figure 3. × 800.

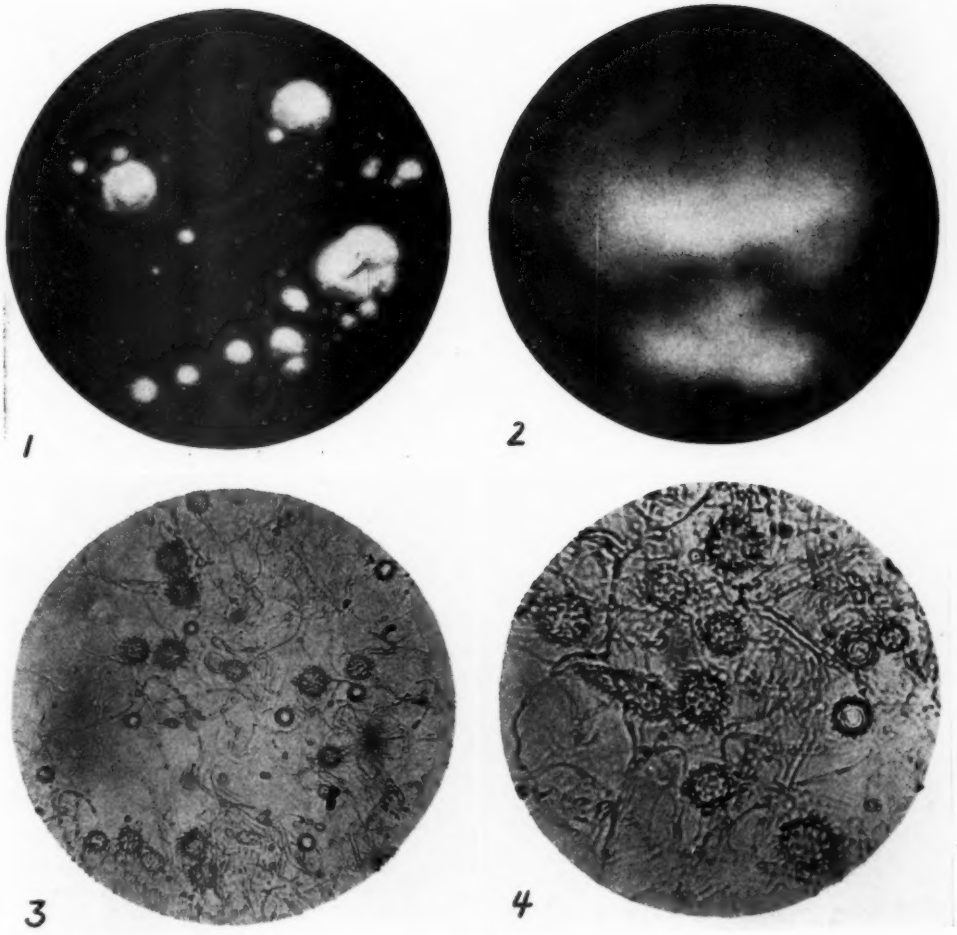


PLATE X

PLATE XI

ACTINOMYCES

The anaerobic type gives rise to the characterisic sulphur granules, gray or yellowish in color, and varying in size, usually less than 1 mm. in diameter. When crushed between a glass slide and cover glass and examined microscopically they are found to be composed of a compact mass of mycelial filaments 0.3 to 1.0 μ in diameter. Around the periphery of this mass, the filaments are arranged radially with their ends expanded into club-like forms 8 to 20 μ in length and 5 to 8 μ in width. The central filaments are Gram-positive, whereas the clubbed ends are Gram-negative. With the aerobic type, the granules, which may or may not be present in the sputum, are composed of a mass of tangled mycelia without evidence of ray- or club-formation. They are Gram-positive.

Artificial Media: Pathogenic actinomyces grow best at 37° C. The rate of growth varies with the different strains considered, usually three to ten days being necessary before the colonies are microscopically visible. The addition of blood and dextrose to the medium facilitates the initial growth of the anaerobic type, while the aerobic type grows well on the usual laboratory media.

The young colonies of both aerobic and anaerobic forms are round and discrete and slowly increase in size. The surface may be smooth, finely granular, wrinkled or nodular (figures 1 and 2). They may develop irregular folds and concentric rings (figure 6), and may at times become heaped. Colonies may become covered with short aerial hyphae and assume a chalk-powdery appearance (figure 5). The color varies—white, gray, yellow or orange.

On Meat Infusion Broth growth develops slowly appearing in from three to ten days, first noted at the bottom of the tube as very small, fluffy or granular colonies, which may be adherent to each other. Surface-growth may be a wrinkled pellicle, at times pigmented.

Microscopically the organisms are markedly pleomorphic, exhibiting filaments, bacilli and coccoid forms (figure 3). The rod-like forms may be slightly curved, or beaded and may have clubbed ends. The filments vary in length, may be straight or wavy, and show true or false branching with tapering ends (figure 4). These organisms are Gram-positive, the filaments and rod-forms often stain irregularly.

The anaerobic type is non-acid-fast, while the aerobic type may or may not be acid-fast.

FIGS. 1 and 2. Colonies of *Actinomyces bovis* grown anaerobically on dextrose blood agar, seven days at 37° C. × 10.

FIG. 3. Gram stain preparation made from a colony grown anaerobically on dextrose blood agar, seven days at 37° C. × 800.

FIG. 4. Gram stain preparation made from broth culture incubated anaerobically for seven days at 37° C. × 800.

FIG. 5. *Actinomyces asteroides* colony, grown aerobically on Sabouraud's agar, seven days at 37° C. magnified. × 4.

FIG. 6. *Actinomyces hominis* colony, grown aerobically on Sabouraud's agar, seven days at 37° C. magnified. × 4.

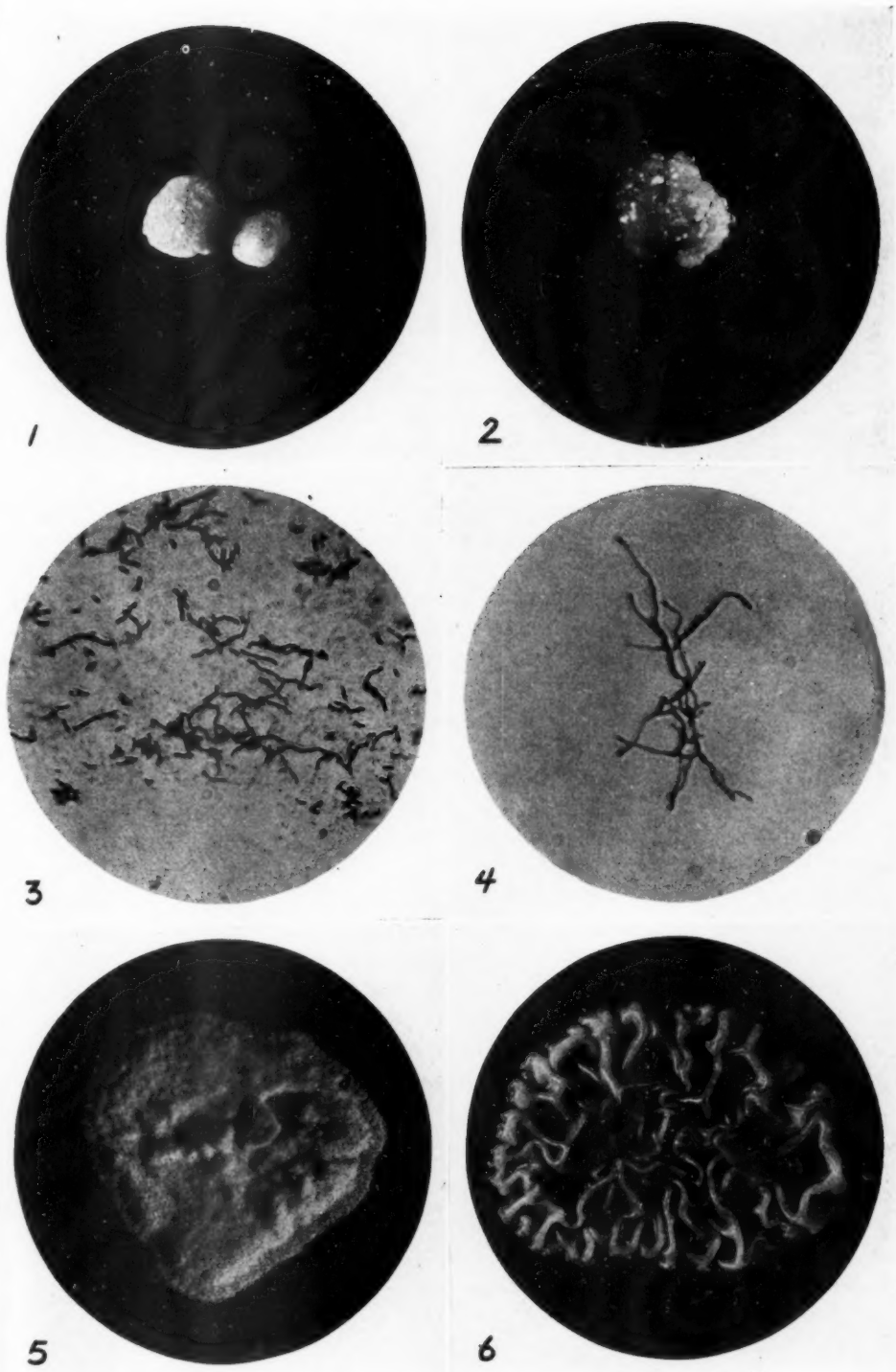


PLATE XI

PRIMARY TUBERCULOSIS[1]

Complicated by Bronchial Tuberculosis with Atelectasis (Epituberculosis)

EDNA M. JONES, T. N. RAFFERTY AND H. S. WILLIS

Clinical pulmonary tuberculosis in children runs a more or less predictable course. Following the primary focus in the lung, there is associated infection and enlargement of the tracheobronchial lymph nodes draining the involved area. In the large majority of cases healing takes place over a period of months or years, with gradual resolution of the pulmonary lesion, return of the lymph nodes to normal or nearly normal size and eventual fibrosis or calcification of the infected tissue—the entire process eventuating in what is known as the primary complex. This course represents the largest group of cases encountered in children.

In a small percent age of cases, due possibly to excessive dose, accidental rupture of a caseous node into a bronchus or blood vessel, "poor resistance", or, possibly, certain intangibles about which we know little, the infection may manifest itself as an extremely severe and even rapidly fatal process. This type and course is also too well known to require elaboration.

A third group includes the rather considerable number of cases of primary tuberculosis which progress and, as "reinfection" tuberculosis, run a checkered and often down-hill course. Extensive pulmonary tuberculosis and tuberculous pneumonia may feature this group.

In the fourth and last group fall the cases that have been called epituberculosis and many other cases of bronchial obstruction (see below) that masquerade as extensive pulmonary tuberculosis or tuberculous pneumonia. A study of cases belonging to this fourth group constitutes the basis of this paper.

The average case in this group presents clinically a rather typical complex. It occurs seldom in adults. It is characterized often by physical signs of lobar consolidation and, as often, by the absence of these signs and indeed of any signs. The X-ray shadow is dense, homogeneous and lobar in extent. The sputum is scanty or absent and nearly always negative to ordinary microscopical examination. The child who has this affection may have had a few days of acute illness at onset but usually he appears in surprisingly good health and exhibits a strong reaction to tuberculin. After months without change, resolution sets in and clinical and roentgenological recovery is the rule. This clinical syndrome was brought to attention first by Eliasberg and Neuland in 1921 (1) and given classical description by them. They applied to it the term epituberculosis.

In spite of this clear-cut picture, wide difference of opinion exists as to its pathological nature. Some have called it gelatinous or tuberculous pneumonia. Some have called it nonspecific pneumonia which behaves in this particular way

[1] From the Wm. H. Maybury Sanatorium (Detroit Municipal Tuberculosis Sanatorium), Northville, Michigan.

only in tuberculous individuals. Some have thought it is due to an extremely high allergic response to small numbers of tubercle bacilli. More recently the view has been expressed, with increasing frequency, that it may be due to none of these factors singly but that it presents, in addition to the primary complex, an added factor of interference with bronchial drainage and aeration which results in atelectasis of the lobe or lobule. Because of its relatively benign nature, not many cases have come to autopsy. However, recent pathological work emphasizes the correctness of this view.

The earlier literature on this subject ascribed the phenomenon of extensive lobar consolidation in children in comparatively good health to the existence of nontuberculous pneumonia which behaved in this particular way by virtue of being "on tuberculous soil." Several observers, Langer (2) and Goldberg and Gasul (3), among others,[2] saw a homogeneous, lobar shadow reappear at the original site after injection of tuberculin. On the other hand biopsy of such a lung revealed typical tuberculous tissue (Rubenstein (4)). Autopsy in several cases (5, 6, 7, 8, 9, 10) with the clinical criteria of epituberculosis revealed tuberculosis, and puncture of the lungs in such cases yielded tubercle bacilli (11, 12, 13). Experimental work in the hands of several authors reproduced slowly clearing tuberculous pneumonia in which X-ray clearing resembled that of the complex under study (14, 15, 16, 17, 18).

It seems incontrovertible that tuberculous lesions of the lungs, even those of large size and extreme density, may resolve. It seems clear, too, that the degree of hypersensitiveness and the size of the infection determine the severity of tissue damage and the degree and rate of clearing. Although such lesions may and do resolve in ordinary tuberculosis, resolution is not the general or average experience. Yet resolution is the usual experience for the group of cases under study and this has led a good many workers to consider whether all, or at least the majority, of these characteristic homogeneous, lobar shadows in clinically well children may not represent atelectasis.

Early in the last decade hints began to filter in which suggested that many of the shadows of epituberculosis were cast by lobar atelectasis and that the latter was caused by bronchial occlusion from encroachment of enlarged tuberculous lymph nodes at the root of the lungs or from actual tuberculosis of the bronchial structures. Morlock and Pinchin (19) removed by bronchoscope tuberculous granulation tissue which obstructed a bronchus in a boy whose film showed a dense lobar shadow. Promptly after removal, the dense shadow disappeared. Numerous others have cited case reports which fit more or less into this aetiological grouping (20, 21, 22, 23, 24, 25, 26, 27).

The pathologist has offered unquestioned proof of the association of atelectasis and bronchial occlusion. For instance, in 1935 Rössle (28) gave a clear description of bronchial distortion and obstruction and pointed to obvious distal atelectasis in cases of this type. Sanes and Smith (29) cited a case of known, long-standing atelectasis produced by calcified tracheobronchial nodes and

[2] According to Goldberg and Gasul at least five other reports published during 1924, 1925 and 1926 carried this same report.

bronchial occlusion, as autopsy revealed fourteen years after clinical onset. Epstein's case of 1922 (7) presented tuberculosis and atelectasis in a pulmonary lobe and occlusion of the bronchus leading thereto. Conclusive cases are those of Terplan (30) who has left no doubt that both enlarged tuberculous tracheobronchial lymph nodes and bronchial tuberculosis may occlude the bronchus and produce temporary or permanent atelectasis.

It is our belief that bronchial obstruction with atelectasis forms the basis for many of these cases and that it occurs in the following manner. The primary focus in the lung is followed soon by disease and enlargement of the lymph nodes at the root and these two factors coexist. There must now be added a third factor—that of interference with bronchial drainage and aeration—to produce the complete picture. This may be brought about by simple mechanical pressure from the enlarged lymph nodes, but probably is more often due to direct extension of the tuberculous process from the nodes into the bronchial walls. This disease may remain in the submucosa or may break through to produce an ulcer or tuberculoma. Tuberculous disease of the bronchial wall, with its attendant collateral inflammation and oedema, leads to paralysis of the ciliary and peristaltic motion in the area and thus inserts a break in the continuity of the drainage mechanism with consequent functional, if not complete structural, blockage. These views grow out of the clinical experience now to be related.

In the five years ending in May, 1941, 716 patients were admitted to the Children's Division of the Maybury Sanatorium. These admissions included all types of tuberculosis occuring in children: parenchymal disease alone, parenchymal and tracheobronchial lymph node disease, disease in the tracheobronchial lymph nodes only, and all types of extrapulmonary tuberculosis. Of this number, 85, about 12 per cent, presented a dense, homogeneous, (usually) lobar shadow in the chest film that is characteristic of so-called epituberculosis. On the basis of this shadow, the tuberculin reaction, history and, in many cases, the physical signs, these children were thought to need bronchoscopic examination. This examination was carried out on 42 of the children but was not done on 43.

The data on the 42 children who underwent bronchoscopic study is given in the two accompanying tables. From table 1 it can be seen that Negro children predominated, the tuberculin reaction was positive in all tested, wheeze was present in more than half, tubercle bacilli were demonstrated by culture in two-thirds. There was multiple lobe involvement in some, variation from normal in size of lobe in several, and, in nearly all, enlargement of the tracheobronchial lymph nodes. Tissue (tuberculoma) removed by biopsy in 9 instances revealed tuberculosis on histological section in each case. The treatment employed, mostly aspiration, cauterization and biopsy, was associated with apparent arrest in a little over one-half. Death occurred in one-fourth of the group. Sputum study included examination of gastric contents and faeces. In earlier parts of the study, examination consisted often of a single culture of the faeces; the later examinations represented a much more intense search for bacilli. These results are in marked contrast to the average report on epituberculosis, in which

the sputum is negative (as are all but 2 in this group of 42 when examined by direct smear only).

TABLE 1

Summary of cases examined by bronchoscope

	NUMBER	PER CENT		NUMBER	PER CENT
Clinical examination			X-ray examination		
Children examined	42	100.0	Size of lobe involved		
			Size decreased	21	50.0
Color: White	9	21.4	Size increased	2	4.8
Negro	33	78.6	Size normal	19	45.2
Sex: Male	20	47.6	Tracheobronchial lymph nodes		
Female	22	52.4	Enlarged	39	92.9
Age range, 1 to 15 yrs.			Normal	3	7.1
Average age, 6.9 years					
Tuberculin test 1:10,000			Bronchoscopic treatment		
Positive	41	97.6	Aspiration	28	
Not done	1	2.4	Application of silver nitrate (tuberculoma and ulcer)	15	
Wheezing present	25	59.5	Biopsy of tissue	9	
Wheezing absent	17	40.5	(Tuberculous tissue found histologically)	9	
Sputum					
Positive by smear	2	4.8	Total treatments per patient 1 to 11		
Positive by culture	28	66.6	Average treatments per patient, 3.1		
Negative	12	28.6	Average duration of treatments, 3.8 months		
X-ray examination					
Location of lobes involved					
Right upper	12	28.6	Results		
Right middle	9	21.4	Apparently arrested	22	52.4
Right lower	2	4.8			
Left upper	10	23.8	In hospital	10	23.8
Left lower	4	9.5	Improving 3		
Right upper and middle	1	2.4	Under active treatment 5		
Right upper, middle, lower	1	2.4	Pulmonary condition satisfactory but extra pulmonary disease 2		
Right middle and lower	3	7.1			
			Dead	10	23.8

The bronchoscopic exploration of these cases presented a series of interesting conditions, often two or even more existing in the same case, as indicated in table 2. In fact, extensive overlapping of lesions occurred so that the bronchi of one child might present narrowing from external pressure (enlarged lymph

nodes), tuberculoma and ulcer and might also be the seat of excessive secretion and mucosal redness and oedema. Of the most important conditions found, narrowing of the lumen by extrinsic pressure from enlarged tracheobronchial lymph nodes was noted in 17, tuberculoma in 15, ulcer in 7. Of the 42, 31 presented one or more of these abnormalities: in 11 the tracheobronchial tree appeared normal.

TABLE 2

This table is so arranged that it indicates the different lesions as they are distributed among the children. It shows the combinations of major lesions—tuberculoma, ulcer, extrinsic pressure—and their association with secretion, redness or oedema

TUBERCULOMA				NO TUBERCULOMA				TOTALS			
Ulcer		No ulcer		Ulcer		No ulcer					
Ext. pr.*	No ext. pr.	Ext. pr.	No ext. pr.	Ext. pr.	No ext. pr.	Ext. pr.	No ext. pr.				
2			1			1	1	5	Oedema	Redness	Secretion
			1		1	1	2	5	No oedema		
	1	1				2	1	5	Oedema	No redness	
2		1				1	8	12	No oedema		
		1				1		2	Oedema	Redness	No secretion
		2						2	No oedema		
			1					1	Oedema	No redness	
	1		1			2	6	10	No oedema		
Totals.. 4	2	5	4		1	8	18	42			

* Extrinsic pressure.

The remaining 43 were not examined bronchoscopically for various reasons. Several were but a few months old: some came under observation early, before the full significance of bronchial obstruction was realized; some presented their clinical or roentgenological evidence only transiently; some died, but many recovered, and the clinical course of many of them paralleled that of those in the group analyzed. This group was not carried as a control series to the group

that went through bronchoscopic exploration and treatment. It is mentioned only to indicate the incidence of this type of affection in the total group of children. This paper deals with an analysis only of the 42 children that were studied bronchoscopically.

In cases of recent obstruction, prompt reopening of airways usually led to prompt relief of the atelectasis. In long standing cases clearing required months; in some, permanent atelectasis and bronchiectasis occurred.

As the tables and case histories show, the syndrome under study has been observed in all stages of its evolution and resolution. Frequent bronchoscopic examination in this series has fortunately revealed examples of all sorts of endobronchial tuberculosis and, in some cases, the pathological process has been followed from a mere bulging of the bronchial wall to tuberculous granulation tissue, tuberculoma and, finally, caseation and ulceration. And, in some of these cases, the onset of the roentgenological shadow so typical of the syndrome has appeared with the increase of bronchial disease as it led to bronchial obstruction and then disappeared following bronchoscopic treatment.

CASE REPORTS

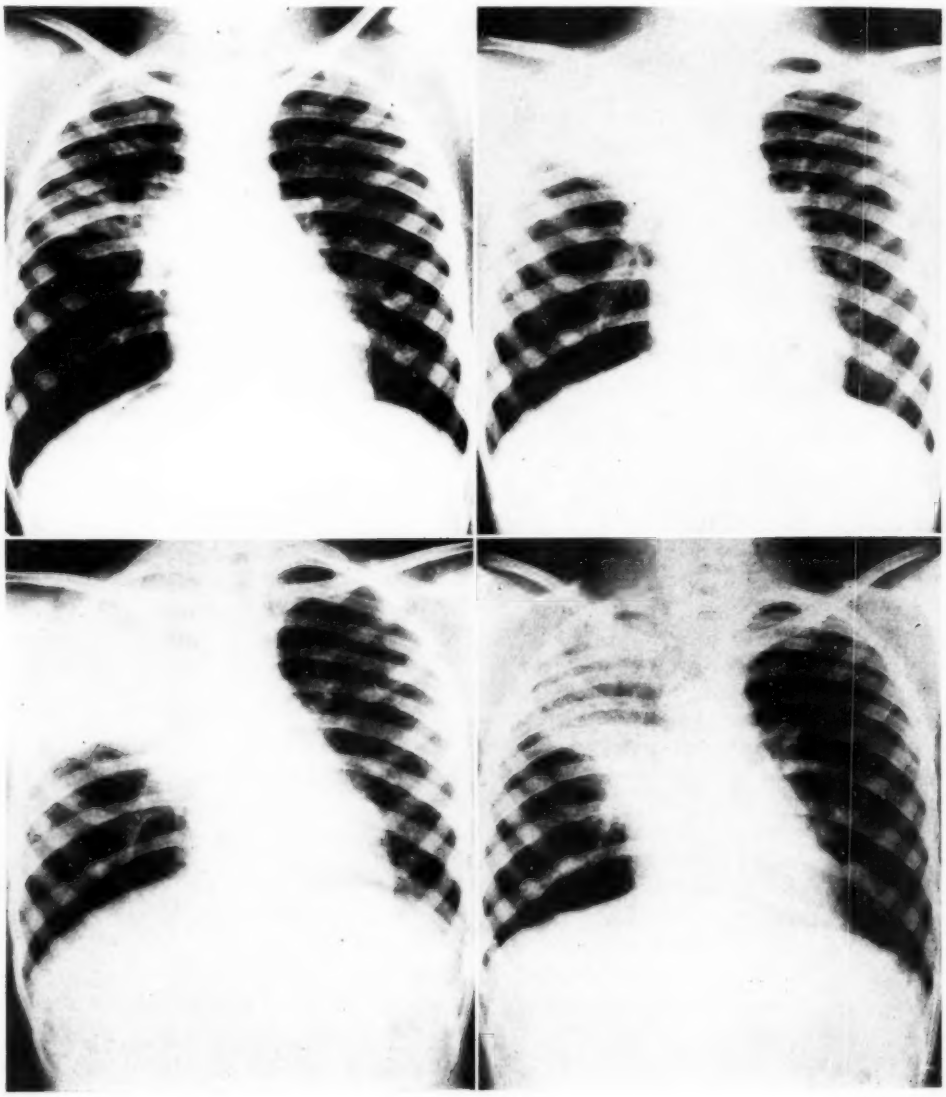
Case 1: E. B., nine year old Negro boy. Admitted July 19, 1940, asymptomatic. History of "asthma" for eight months. He was exposed to his mother who died of tuberculosis. His tuberculin reaction was positive to 1:10,000 O.T. Temperature was 99.6°F., white count, 10,800 with 38 per cent polymorphonuclears.

Admission film (figure 1, July 20, 1940) showed "hilar flare" and enlargement of tracheobronchial lymph nodes. Three weeks after admission the boy became acutely ill with temperature up to 103°F., wheezing, tachycardia, tachypnoea, abdominal pain. The white count rose to 26,000 with 85 per cent polymorphonuclears. Fluoroscopic examination revealed a dense, homogeneous shadow over the right upper lobe, as shown in figure 2, and shifting of the mediastinum on inspiration toward the affected side. Bronchoscopic examination (August 10, 1940, date of figure 2) showed a bulging mass on the lateral wall of the right main bronchus due to extrinsic pressure. Anterior and inferior to this a tuberculoma overhung the right upper lobe bronchus; the mucous membrane was oedematous; secretions were aspirated.

Symptoms remained unchanged until eleven days later when fever reached 105°F. and patient had a chill and an increase in X-ray shadow, as indicated in figure 3 (August 24, 1940). Because of reappearance of symptoms, bronchoscopic aspiration was done on September 5. On September 26 lesion in fluoroscope appeared as shown in figure 3. Same day thick secretion was aspirated through the bronchoscope and the tuberculoma was removed partially. This brought symptomatic relief and marked regression of shadow, as shown in figure 4, which was taken two days after bronchoscopy. In the next three months bronchoscopic treatment by application of 30 per cent silver nitrate and further removal of the tuberculoma was done several times and was associated with development of a clean scar and clearing shadow in the chest film. The extrinsic pressure became less marked. Sputum was positive once out of six cultures. At this time patient was afebrile and his white count was 15,150. This is a good example of "wet" atelectasis, that is, atelectasis without decrease in the volume of the involved lobe.

Case 2: W. W., Jr., a six year old white boy. He was first seen in the out-patient department on November 15, 1937. His only symptom was cough of two weeks' duration.

His white count was 8,350. An X-ray film showed lymph node enlargement and a fibrous parenchymal lesion in the first interspace, right. Another X-ray film (May 7,



FIGS. 1–4

FIG. 1. Case 1. Upper left. Admission film, July 20, 1940.

FIG. 2. Case 1. Upper right. Film three weeks after admission (August 10, 1940) when patient was acutely ill.

FIG. 3. Case 1. Lower left. Film taken August 24, 1940, after further exacerbation.

FIG. 4. Case 1. Lower right. Film taken September 28, 1940, two days after removal of tuberculoma.

1938) six months later (figure 5) showed the parenchymal lesion unchanged and some "flare" in right at the hilum. At about this time wheezing was present.

He was admitted to the Sanatorium on May 23, 1938. His admission film, two weeks after the previous film, showed atelectasis of right upper lobe with shifting of fissure upward and disappearance of parenchymal lesion into atelectatic area. Pre-bronchoscopic X-ray film (figure 6, June 4, 1938) showed no change. Bronchoscopy on June 9, 1938 revealed a tumor the size of a small pea protruding from the right upper lobe bronchus, with a necrotic tip; it was oedematous. Biopsied portion showed tuberculous tissue histologically. Bronchoscopy on June 23, 1938, two weeks later, presented a much smaller mass. It was observed to be moving back and forth with respiration. There was no more oedema. More material was removed and the base of the intrabronchial mass was cauterized. Figure 7 (June 30, 1938) taken one week after the second bronchoscopy, showed the lung had returned to its original appearance with the fissure at its normal level and the parenchymal lesion in first interspace was seen again. Bronchoscopy on July 7, 1938 showed no evidence of the former lesion. An X-ray film taken nine months later showed further clearing of the primary focus, the fissure shadow and further reduction in size of the tracheobronchial lymph nodes. Sputum was negative by all methods. The patient was discharged as apparently arrested. He has led a normal life since. He was seen in January, 1942, three years and eight months after admission. His X-ray film was negative except for small, dense, fibrous lesion at the site of the original pulmonary focus. A white blood count was not done after admission. The temperature was always within the limits of normal. This represents an example of "dry" atelectasis.

Case 3: R. W., a three and one-half year old Negro boy. Admitted January 25, 1939, with cough, weakness, wheezing for ten months. Past history of "pneumonia" twice, measles, otitis media and no history of exposure. His tuberculin test was positive to 1:10,000 O.T. His white count was 9,200. He had no fever. His admission X-ray film showed atelectasis in the lower lung field and hilar lymph node enlargement. A lateral film suggested that this atelectatic area was in both middle and lower lobes. Symptoms at that time were mild, with no wheezing.

Bronchoscopy three weeks after admission showed partial obstruction of the main stem bronchus on the right and a tuberculoma protruding from the middle lobe bronchus. This was partially removed but some tuberculous granulation tissue was left. This was touched with 30 per cent silver nitrate. Gastric lavage done at this time yielded a culture of tubercle bacilli.

Bronchoscopy on March 2, 1939 showed granulation tissue still plugging the middle lobe bronchus. More tissue was removed and the base was again cauterized. Bronchoscopy on March 30, 1939 showed granulation tissue but no tuberculoma; this was cauterized again with silver nitrate. At this time the base could be seen more clearly and appeared to be in the right main bronchus, just above the middle lobe bronchus. Bronchoscopy on May 4, 1939 showed no evidence of previous bronchial disease. Secretions were aspirated. An X-ray film four months after admission showed moderate clearing of lesion at the base. An X-ray film nine months after admission showed fibrosis in lower lung field, smaller nodes and no collapse. Another X-ray film sixteen months after admission, showed marked decrease in the size of the lymph nodes and fibrosis in the lower field. Bronchoscopy (September 26, 1940) one year, eight months after admission, one year, seven months after the first bronchoscopic examination, showed normal tracheobronchial tree. No further white blood counts were done. The patient had occasional slight fever associated with recurrent otitis media. Patient was discharged one and one-half years after admission and remained quite well after another one and one-half years.

Case 4: D. W., a three and one-half year old Negro boy, admitted December 29, 1937 with a history of exposure to a tuberculous uncle. His tuberculin test was positive to 1:10,000 O.T. He had cough and cervical adenitis of unknown duration. His white count was 16,200 with 38 per cent polymorphonuclears. He had fever up to 99.6°F. during the first few days, none thereafter. Admission X-ray film showed widened mediastinal shadow and a dense shadow in the area of the right lower lobe. Bronchoscopic examination revealed a tuberculoma occluding the right main bronchus. Four bronchoscopic examinations, the last one almost a year after the first, showed complete healing following ulceration and topical application of silver nitrate. X-ray examination fifteen months after admission showed residual atelectasis and moderate bronchiectasis demonstrated by lipiodal. Sputum was negative by all means of study. He was discharged as apparently arrested. The condition of the patient remained unchanged and so did his X-ray appearance two and one-half years later. This indicates atelectasis of long standing with permanent bronchiectasis.

Case 5: E. W., a five year old Negro girl with a sudden onset of disease in December, 1940, with fever to 106°F. for several days; she was listless but without cough. Her tuberculin reaction was positive to 1:10,000 O.T. Her white count was 9,000, with 79 per cent polymorphonuclears. An X-ray film showed consolidation of the left upper lobe, thought to be atelectasis. Her sputum was positive by culture, probably indicating a primary focus in the collapsed lobe. Bronchoscopic examination January 16, 1941 showed an extrinsic pressure on the left main bronchus and thick secretions. For two months breath sounds were audible faintly, later they were completely absent for four months, during which time gastric lavage was negative. Clinical course remained unchanged until May, 1941 when severe loose cough and wheezing appeared and breath sounds were again audible. An X-ray film showed partial aeration of upper lobe and spread of the disease to the left lower lobe and, later, to the right lung. Bronchoscopic examination revealed large amounts of secretion in trachea and left bronchi but no bulge from extrinsic pressure. The disease became generalized and autopsy in January, 1942 showed extensive enteritis, peritonitis and marked tuberculosis of mesenteric lymph nodes in addition to far advanced pulmonary disease. No encroachment on the lumen was found at postmortem examination. This case is thought to represent extensive primary tuberculosis in the left upper with associated enlargement of the tracheobronchial lymph nodes which, with thick secretion, produced bronchial obstruction for a period of several months. Meantime primary pulmonary disease progressed. The bronchial obstruction resolved, as indicated by bronchoscopic examination and autopsy.

Case 6: V. S., an eight year old white girl, admitted July 18, 1935. Her white count was 8,450 with 72 per cent polymorphonuclears. There was no history of exposure. Her tuberculin was positive to 1:10,000 O.T. Onset was in February, 1935 with cough, headache, drowsiness. An X-ray film showed parenchymal infiltration in the region of the right middle lobe and enlarged lymph nodes. Her course remained essentially unchanged, but film of March 18, 1936 (figure 8), eight months later, showed increase in

FIG. 5. Case 2. Upper left. Outpatient film, May 7, 1938.

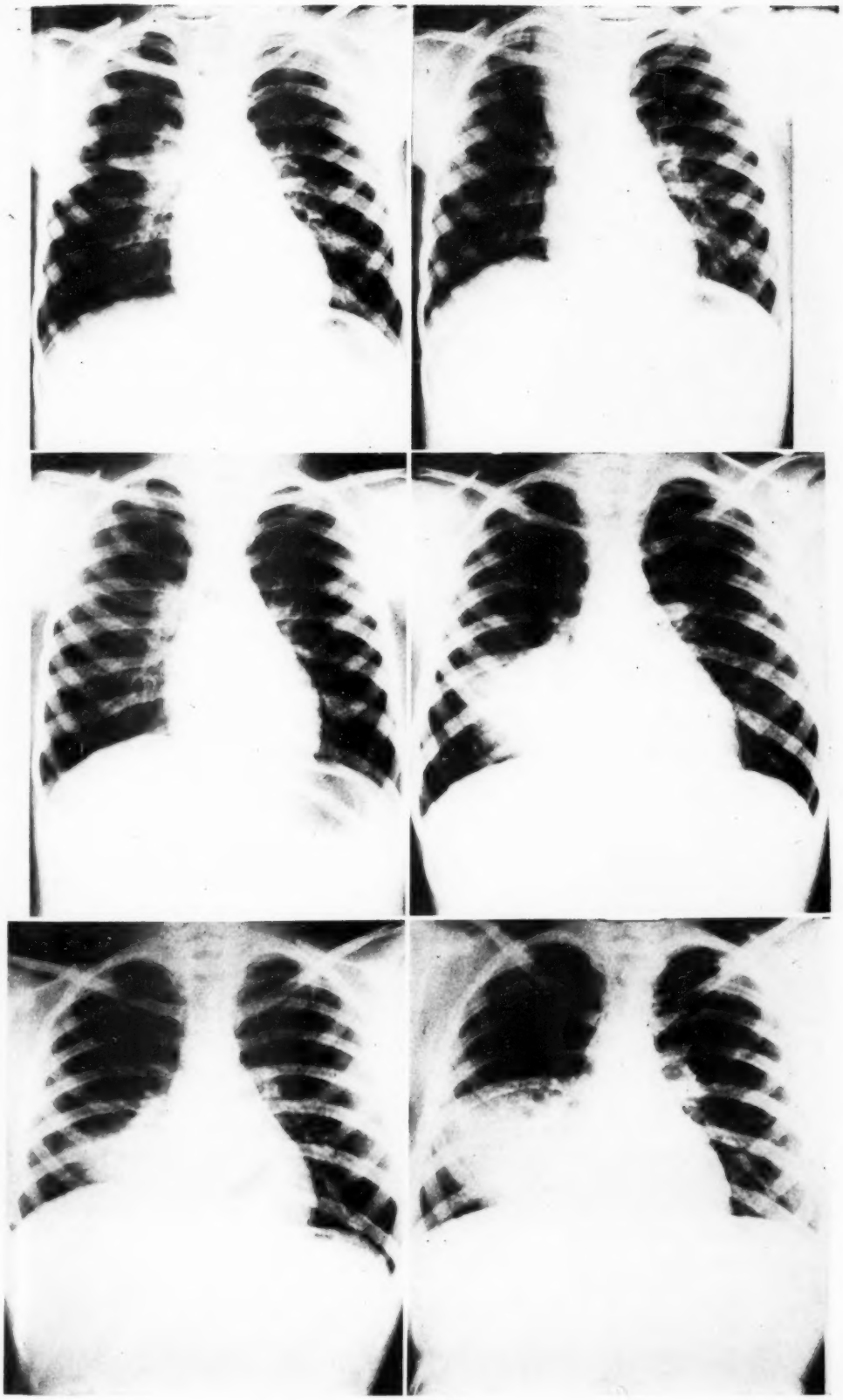
FIG. 6. Case 2. Upper right. Film taken one month after that shown in figure 5 (June 4, 1938). Tuberculoma found.

FIG. 7. Case 2. Center left. Taken June 30, 1938, one week after removal of tuberculoma.

FIG. 8. Case 6. Center right. Film taken March 18, 1936, before bronchoscopic examination.

FIG. 9. Case 6. Lower left. Taken toward end of bronchoscopic treatment.

FIG. 10. Case 6. Lower right. Taken May 30, 1938 after exacerbation.



FIGS. 5–10
401

infiltration of right lung. A lateral film of June 23, 1936 showed this to be in the right middle lobe. Because of fluctuating lesion, bronchoscopy was done in October, 1936 and a tuberculoma was found in the right main bronchus near the middle lobe bronchus. Biopsy showed tuberculous granulation tissue. Removal and cauterization were done at eight different sittings. White blood count remained practically unchanged. Temperature was frequently up to 99.6° or 100°F. at this time. She was afebrile thereafter until first discharge.

The X-ray film of April 26, 1937 (figure 9), taken after six months of treatment, revealed continued improvement. She was discharged in June, 1937. Patient was home and well for eight months until May, 1938 when she developed acute symptoms of pain in the side, cough, fever to 104°F. and purulent sputum. A film at this time (May 23, 1938) showed marked increase in the shadow at the site of the original disease and she was rehospitalized. Film of May 30, 1938 (figure 10) showed many areas of rarefaction in the involved area and her sputum was positive. White count was 18,000 with 82 per cent polymorphonuclears. This case represents a reinfection type tuberculosis in the area previously occupied by atelectasis (and undoubtedly some primary disease as well).

Bronchoscopy done on June 9, 1938 showed only small bronchial scar. Pneumothorax was then started and continued without complication until discharge, twenty-two months later.

Bronchoscopy on February 22, 1940 again was negative. Patient's status as of January, 1942 is unchanged.

DISCUSSION

There are many variations in the course of primary tuberculosis which are brought to light only through frequent X-ray examinations. Of the cases under study, 52 per cent recovered, 24 per cent died, the remainder are still hospitalized. Deaths fell into three groups: (*1*) those that experienced exacerbation of the pulmonary focus either during the atelectasis or after it; (*2*) those that developed wide-spread pulmonary tuberculosis from ruptured caseous tracheobronchial lymph nodes; and (*3*) those in whom extrapulmonary tuberculosis appeared and became progressive.

Pulmonary tuberculosis of pneumonic or lobar type and epituberculosis may present indistinguishable clinical syndromes. However, the more severe symptomatology and progressive course of the one usually stand in clear contrast to the relative asymptomatology (except during the first few days) and the stationary or disappearing X-ray shadow of the other. In the differentiation between the two, time is of the essence, because patients with epituberculosis (atelectasis) will most often recover and those with tuberculous pneumonia will usually progress to death. This thesis points to a logical and, the authors think, accurate explanation for the behavior of this group of children and indicates the need of judicious bronchoscopic study for the full implication of such a clinical syndrome.[3]

Atelectasis associated with partial bronchial obstruction from extrinsic pressure behaves irregularly. Secretion may fill the lumen at the point of pressure and thus lead to total lobar atelectasis. Release of secretions by excessive

[3] Emphasis may be properly placed on *judicious* bronchoscopic examination. This paper is certainly not a plea for the indiscriminate use of this instrument. In such cases fluctuation in condition occurs often. Our experience with this group of cases indicates that collapse therapy is not only contraindicated but may be definitely harmful.

cough or instrumentation reopens the airways temporarily for aeration, with resulting fluctuation in the density of the X-ray shadow cast by the involved lobe. Prolonged partial obstruction of this type or prolonged total obstruction is often associated with secondary infection of the lobe so that residual scars may prevent forever the return to normal appearance or function.

In addition, tuberculous involvement of the bronchus either as ulcer, tuberculoma or infiltration from neighboring tuberculous lymph nodes may affect the lymphatic circulation in the bronchus and produce lymph stasis in the lung which eventually produces a dense shadow of the lobe.

In attributing much of this phenomenon to atelectasis, it is admitted that most of these cases present none of the so-called classical signs of atelectasis, such as elevated diaphragm, narrowed interspaces or shifted mediastinum. However, it is becoming increasingly obvious that these phenomena actually occur only in a small percentage of cases of bronchial obstruction, and that atelectasis with marked diminution of lung volume occurs only when the parenchyma is essentially normal or when a main or lobar bronchus is obstructed.

If the bronchus is occluded gradually and parenchymal tuberculosis is present, adjustments are made and the outpouring of fluid into the tissues may be more rapid than the absorption of the air, so that the volume of the lobe may be as great as and occasionally even greater than that of the normal lobe. The signs mentioned above are valuable when they occur but should not lead one to dismiss the diagnosis of atelectasis merely because they are absent.

This brings up the question of the propriety of the terms "dry" and "wet" atelectasis. Many will not concur in such designations. But it seems clear from this study that cases with relatively fibrous, well invested pulmonary lesions and enlarged tracheobronchial lymph nodes experience typical atelectasis with marked lobar shrinking when the bronchus is occluded. The air is absorbed and the lobe collapses promptly. On the other hand, the lobe which is the seat of an active or relatively fresh lesion may present conditions in which the ventilated air fails to reach the patent capillary bed. Such a lobe both allows absorption of air less quickly and produces secretions (to become sputum) quite readily. The interplay between these forces tends toward replacement of the air with fluid and thus leads to a large, wet lobe. These relationships appear to be of particular importance in cases in which the obstruction develops gradually. Such a filled or "drowned" lobe may not be atelectatic in the technical sense of "imperfect expansion" but it is as inadequate as the shrunken lung, is produced by bronchial obstruction and the two may be thought of as representing the two extremes of pulmonary airlessness associated with bronchial obstruction in tuberculosis. However this may be or by whatever name we label the phenomenon, the matter of importance is that bronchial obstruction may produce a functionless lobe that is shrunken and without air or one that is of normal or increased size and is without air, fluid having replaced it.[4]

[4] Two interesting papers have appeared recently in the English literature which discuss the clinical significance and point to the essential pathology of bronchial obstruction. One is by Morlock (31) who cited several cases pertinent to the subject in hand and has emphasized its importance. Allison (32) has drawn attention to several types of disease causing bronchial obstruction and has shown the morbid anatomy underlying them.

CONCLUSIONS

1. Pulmonary tuberculosis in children presents rather a kaleidoscopic picture. The majority of cases pass through the affection in a relatively uneventful way to recover and to present finally the end picture of the primary complex. Some develop extrapulmonary disease. Some run a checkered course in which tuberculous pneumonia or extensive pulmonary tuberculosis is diagnosed. Among the latter a considerable per cent are diagnosed erroneously, for many of them represent not tuberculosis as the main disorder but pulmonary atelectasis and belong to the group heretofore classified as epituberculosis. In addition to these, a fair number develop symptoms that have led directly to the diagnosis of epituberculosis.

2. Evidence has been presented in this discussion in support of the hypothesis that the syndrome is essentially a lobar or lobular atelectasis, occurring as a result of interference with pulmonary aeration and drainage; this interference arises during the active phase of the primary complex and most frequently is a direct result of extension of the tuberculous process into the bronchial wall from infected peribronchial lmyph nodes. It may consist of simple mechanical obstruction by an enlarged lymph node or tuberculoma; or it may be due to interference with ciliary and peristaltic motions. Repeated correlations of bronchoscopic and roentgenographic evidence, as described, are thought to furnish definite proof of the validity of this hypothesis.

3. Atelectasis occurs in children with primary tubereulosis much more frequently than is usually thought and its possibility should always be borne in mind in the child whose pulmonary film shows a dense, homogeneous shadow.

4. This term epituberculosis has for many years been used to designate a clinical syndrome of which the essential feature is lobar consolidation, benign in nature and occurring in tuberculin positive children. The pathological basis for this phenomenon has never been understood clearly.

5. In view of these findings it is suggested that the indefinite and confusing term "epituberculosis" is no longer needed and should be abandoned.

SUMMARY

During a five-year period ending in May, 1941, 716 patients were admitted to the Children's Division of the Wm. H. Maybury Sanatorium. Of this number 85, or 12 per cent, presented the dense, homogeneous shadow of so-called epituberculosis. Bronchoscopic examination was made on 42 of these. Most of those not examined in this way entered the Sanatorium early in the series, before the true significance of the syndrome was realized, were infants, or presented mild symptoms. The examinations revealed the following:

In 31, or 74 per cent, bronchial distortion or disease was present chiefly as narrowing of the lumen from pressure by enlarged lymph nodes at root, tuberculoma, ulceration. Oedema, redness and secretions were present in many of the cases. (Several children presented more than one of these conditions.)

In 11 no bronchial abnormality could be found.

SUMARIO

En el quinquenio terminado en mayo 1941, se recibieron 716 enfermos en la Sección de Niños del Sanatorio Wm. H. Maybury. De ellos 85, o sea 12 por ciento, presentaban la sombra homogénea y espesa de la llamada epituberculosis. En 42 se realizó un examen broncoscópico. La mayor parte de los que no fueron examinados de este modo, o bien ingresaron en el Sanatorio al principio de la serie, antes de comprenderse el verdadero significado del síndrome o eran lactantes, o presentaban síntomas más leves. Los exámenes revelaron lo siguiente:

En 31, o sea 74 por ciento, había deformación bronquial patológica, consistente principalmente en estrechamiento debido a la presión ejercida por los ganglios linfáticos hipertrofiados en la raíz del bronquio, o por tuberculoma o úlcera. En muchos casos había edema, rubefacción y secreción, y varios niños presentaban más de uno de esos estados.

En 11 no pudo observarse anomalía bronquial.

Note: The extensive bronchoscopic work on the cases here reported was done by Dr. Wm. M. Tuttle who is on the consulting staff. Without this valuable corollary, the study and its conclusions would have not been possible.

REFERENCES

(1) Eliasberg, H., and Neuland, W.: Die epituberkulöse Infiltration der Lunge bei tuberculösen Säuglingen und Kindern, Jahrb. f. Kinderh., 1920, *93*, 88. (Also Ibid., 1921, *94*, 102).

(2) Langer, H.: Die Spezifität rückbildungsfähiger Lungeninfiltrate bei kindlicher Tuberkulose (sog. epituberkulöse Infiltration), Ztschr. f. Kinderh., 1923, *34*, 142.

(3) Goldberg, B., and Gasul, B. M.: Epituberculosis, Am. J. M. Sc., 1930, *180*, 824.

(4) Rubenstein, H.: Zur pathologischen Anatomie der Lungeninfiltrierungen, Beitr. z. Klin. d. Tuberk., 1928, *70*, 773.

(5) Grävinghoff: Zur Kenntnis der "epituberkulösen" Infiltration, Monatschr. f. Kinderh., 1921, *21*, 447.

(6) Engel: Über Paratuberkulöse Lungenkrankungen, Berl. Klin. Wchnschr., 1921, *58*, 887. (Quoted from Goldberg and Gasul (3).)

(7) Epstein, B.: Zur Kenntnis der epituberkulösen Infiltration der kindlichen Lunge, Jahrb. f. Kinderh., 1922, *99*, 54.

(8) Schlack: Beitr. z. Klin. d. Tuberk., 1926, *63*, 280. (Quoted from Oppenheimer (16).)

(9) Leitmann: Ibid., 1928, *69*, 606. (Quoted from Oppenheimer (16).)

(10) Sonnenfeld: Ibid., 1928, *70*, 773. (Quoted from Oppenheimer (16).)

(11) Görter, E., and Lignac, G. O. E.: Acta paediat., 1930, *10*, 87. (Quoted from Spence (12).)

(12) Spence, J. C.: Benign tuberculous infiltration of the lung (epituberculosis), Arch. Dis. Child., 1932, *7*, 1.

(13) Loots: South African M. J., 1933, *7*, 214. (Quoted from Oppenheimer (16).)

(14) Austrian, C. R., and Willis, H. S.: The pulmonary effects of intratracheal injections of Old Tuberculin in rabbits, Am. Rev. Tuberc., 1926, *14*, 306.

(15) Willis, H. S.: The specificity of pulmonary consolidation in tuberculous patients (epituberculosis), Am. J. Roentgenol., 1934, *31*, 721.

(16) Oppenheimer, Ella H.: Experimental studies on the pathogenesis of epituberculosis, Bull. Johns Hopkins Hosp., 1935, *57*, 247.

(17) Burke, H. E.: Tuberculosis in rabbits, Am. Rev. Tuberc., 1940, *42*, 343, 499.

(18) Reichle, H. S.: Resolving exudates in pulmonary tuberculosis of childhood, Am. J. Dis. Child., 1933, *45*, 307.

(19) Morlock, H. V., and Pinchin, A. J. S.: Epituberculosis—a query as to the entity of this condition, Lancet, 1933, *1*, 1114.
(20) Korol, E.: Atelectasis in pulmonary tuberculosis, Am. Rev. Tuberc., 1931, *23*, 493.
(21) Sweany, H. C.: The tuberculosis problem viewed in the light of recent pathologic studies, Minnesota Med., 1939, *22*, 595.
(22) Macpherson, A. Margaret C.: Primary tuberculosis of the lung in children, Brit. J. Tuberc., 1939, *33*, 79.
(23) Hennell, H.: Massive pulmonary atelectasis (collapse), Arch. Int. Med., 1929, *44*, 604.
(24) Eloesser, L.: Bronchial stenosis in pulmonary tuberculosis, Am. Rev. Tuberc., 1934, *30*, 123.
(25) deBruin, M.: Epituberculosis, Arch. Dis. Child., 1936-37, *11-12*, 65.
(26) Lerche, W.: Infected mediastinal lymph nodes as a source of mediastinitis, Arch. Surg., 1927, *14*, 285.
(27) Riggins, H. McL.: Tracheobronchial tuberculosis, Tr. Nat. Tuberc. A., 1939, *35*, 341.
(28) Rössle, R.: Die pathologisch-anatomischen Grundlagen der Epituberkulose, Virchows Arch., 1935-36, *296*, 1.
(29) Sanes, S., and Smith, W. S.: Massive pulmonary atelectasis following bronchial obstruction in tuberculosis, Am. Rev. Tuberc., 1937, *36*, 727.
(30) Terplan, K.: Anatomical studies on human tuberculosis, Supplement to Am. Rev. Tuberc., August, 1940.
(31) Morlock, H. V.: Bronchial obstruction in pulmonary tuberculosis, Tubercle, 1941, *22*, 207.
(32) Allison, P. R.: Bronchial obstruction in pulmonary tuberculosis, Ibid., 1941, *22*, 231.

THE CLINICAL EPISODE IN TUBERCULOSIS AND THE METEOROLOGICAL ENVIRONMENT[1]

WILLIAM F. PETERSEN

In a preceding paper (1) the biochemical background associated with change in the clinical status of the tuberculous patient has been outlined, and the intricate relation of the meteorological rhythm to the biological rhythm of the patient has been demonstrated.

It was shown that the tissue status associated with clinical activation is one that normally follows anoxia and is basically a fatigue state—with capillaries more permeable, vascular and connective tissue tone lessened, digestive processes accentuated, the pH of the venous blood lowered, carbon dioxide content increased, etc. On the other hand, the phase associated with lessened clinical activity involved a relative sympathicotonia. Exaggeration of this state may lead to anoxia, particularly in the peripheral tissues, the accumulation of capillary-active substances, and these in turn to the fatigue state and activation.

Environmental tranquillity is obviously desirable in the active stages, environmental turbulence may be harmful. Individual weather episodes, in other words, the passage of atmospheric fronts, may swing the biochemical balance in wide amplitudes and in so doing, biochemical levels may be reached that will either be equilibrated very slowly or not at all.

Obvious changes in the clinical picture reflect such biochemical and biophysical phenomena. When, therefore, we have available a carefully dated clinical record, the study of the one environmental factor which we can at least in part relatively evaluate and relate chronologically, namely the meteorological condition, frequently affords an interesting sidelight into the picture of the complex forces which ultimately determine the outcome of the particular disease in the particular patient under consideration.

Inasmuch as we can often identify brusque changes in the environmental conditions in connection with clinical change, the significance of the weather factor becomes more evident, the more so since it has been so thoroughly neglected in the past century.

Because weather records are readily available, it becomes a very simple matter to relate any clinical record to a meteorogram of the time.[2]

I have selected a case record of Blatt and Greengard (2) dealing with *Pericarditis as a Primary Clinical Manifestation of Tuberculosis in Childhood.* The case record follows:

History: Walter H., colored, aged nine, was admitted to the Children's Ward, Cook County Hospital, April 27, 1925, **(4)**. He had been in good health until two **(1)** weeks previously, when he had begun to cough. A week later, **(2)** he had complained of head-

[1] From the Department of Pathology, Bacteriology and Public Health, University of Illinois College of Medicine, Chicago, Illinois.

[2] Those here used indicate only the maximum and minimum temperature in degrees Fahrenheit, the barometric pressure in inches, and the precipitation (black bars over the date line). Clinical episodes related in the text are indicated by circled numbers.

ache and had had a slight rise in temperature in the evening. Thirty-six hours before admission, **(3)** he was seized with sharp, knifelike constant pain in the left side of the chest, which was aggravated by respiration.

His previous illnesses were mumps, measles and colds. He had never had a severe sore throat, chorea or other rheumatic manifestations. History of contact with tuberculosis was not obtainable.

A diagnosis was made of pericarditis with effusion of questionable type.

Course of illness: On April 30, the friction rub was diminished, and the heart tones were distant. Fifty cubic centimeters of a blood-tinged fluid was withdrawn from the pericardium; it had a specific gravity of 1.020 and contained albumin and numerous red cells. Organisms were not found on the smear. Cultures of this fluid and all subsequent specimens were sterile; smears for tubercle bacilli were constantly negative. At this time, a diagnosis of tuberculous pericarditis was suggested, and later confirmed by a positive Pirquet test and positive results from inoculation of guinea pigs.

Subsequently the child had an elevated temperature continuously; it was remittent, ranging from 99° to 100°F. in the morning to 103° to 104°F. in the evening. Until July 18, there was marked dyspnoea necessitating pericardial tapping at weekly intervals. The amount of fluid removed varied from 100 to 850 cc., and the blood in the fluid gradually diminished. On July 12, the exudate was a clear amber and remained so. Clinical improvement dated from this time, and on July 18 the last tapping resulted in 350 cc. of a clear amber fluid. The total amount of fluid withdrawn during the ten punctures amounted to 5,130 cc. The patient was discharged from the hospital on September 9, with an enlarged heart with distant heart tones but no murmurs or friction rubs.

Roentgen-ray results corroborated the size of the pericardial effusion, showing slight hilum shadows and no other abnormalities in the lungs.

Admission to Municipal Tuberculosis Sanitarium: His subsequent history was obtained from the social service department of the Cook County Hospital, and Dr. K. J. Hendrickson, of the Chicago Municipal Tuberculosis Sanitarium. He was hospitalized at St. Luke's Hospital on January 7, 1926, **(5)** and discharged from there to the Municipal Tuberculosis Sanitarium in April, where he died on June 7. **(6)**

When we examine the meteorogram (figure 1) we note the following associations: **(1)** the beginning of cough and the onset of illness on April 12, 1925 ooccurred at the time when temperatures dropped abruptly from a high temperature on the preceding day, with almost an inch of precipitation at the time. **(2)** Headache occurred with a sharp polar crest; a cyclonic low had been evident on the 19th of the month, with this there was rain; then a polar air mass passed over Chicago, with temperatures dropping rapidly and barometric pressure increasing more than 0.6 of an inch. **(3)** Sharp pain on the left side of the chest began with another major change in environmental temperatures from a maximal high of about 85°F. and then followed by a rapid shift to cold weather. Hospitalization followed immediately with this (4), occurring at a crest of barometric pressure.

Hospitalization at St. Luke's Hospital on January 7 **(5)** occurred with a polar crest, and death **(6)** occurred with the passage of a polar front after a period when barometric pressures had been very low. In all this it becomes evident that the sick organism had to adjust to a rapid and marked change in environmental conditions.

I have reproduced the detailed clinical report of Blatt and Greengard to illus-

trate the close association of an environmental change and the reflection of the change in air mass in the clinical picture. To the clinician who thinks in the static terms of the final pathological picture, such an association at first glance seems preposterous. But consideration of the fact that even the sheltered individual must constantly react to the air mass in which he exists; that life in this region of the world where a cyclonic atmospheric circulation prevails, predicates continuous change in autonomic mechanisms of adjustment—these facts will soon bring realization that a focal reaction is to be expected. The very fact that certain tissues are diseased involves the concept that they will be less able to conform to the pattern of change in the organism as a whole if they cannot readily adjust either to change in the pH, to change in water balance, to change in tissue turgor, etc.—such a focus must come to the attention of the organism

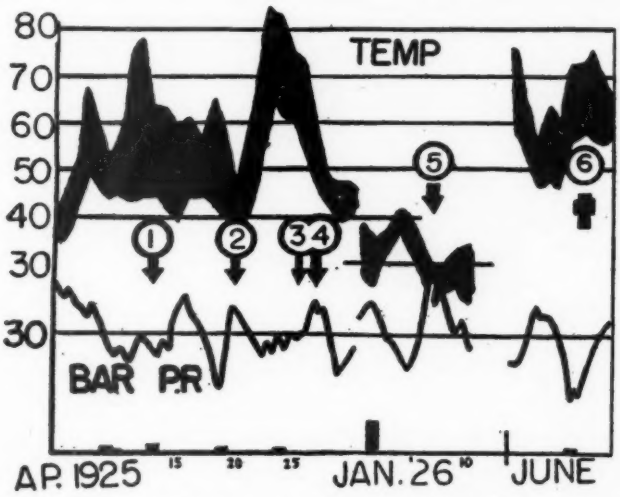


FIG. 1. Meteorogram to illustrate the clinical events in the case of Drs. Blatt and Greengard.

as a whole because of pain, swelling, reference of clinical symptoms to adjacent organs, etc.

GENERALIZED TUBERCULOSIS OF THE LYMPH NODES AND MULTIPLE CYSTIC TUBERCULOSIS OF THE BONES

Jacobsen (3) has detailed the case histories of a family in whom *Generalized Tuberculosis of the Lymph Nodes and Multiple Cystic Tuberculosis of the Bones* occurred. The record is as follows:

Case 1: S. M. R., Negro girl, admitted to the Children's Hospital on May 7, 1929, at the age of eight years, complaining of lumps in neck and sore eyes. She died February 11, 1935.

Family history: Father: In July, 1930, at the age of thirty-five years he applied at the out-patient department of the Buffalo City Hospital because of cough and loss of weight. X-ray examination revealed a shadow in the right apex and a diagnosis of

pulmonary tuberculosis was made. Symptoms were slowly progressive. In January, 1934, because of weakness, shortness of breath, and night sweats he was admitted to the hospital. Tubercle bacilli were found in the sputums on five occasions. He died May 11, 1934, **(1)** three weeks before the death of his daughter (case 2).

Mother, aged thirty-six years (in 1929), was living and apparently well but felt "run-down." Blood Wassermann test negative. X-ray picture of chest showed evidence of old healed tuberculosis. Epitrochlear nodes were enlarged.

Past history: Birth and development as an infant were normal. The only illnesses were measles and pertussis. The child was apparently in good health until the onset of the present condition.

Present illness: About one year before admission to the hospital the mother first noticed lumps in the child's neck. These had slowly grown larger and more numerous. For the same period of time the left eye had been sensitive to light and had been inflamed and swollen periodically. There were no other complaints.

On March 16, 1933, **(2)** the left elbow became enlarged and hot to touch, and a fusiform swelling of the left third finger appeared. The latter was incised, and no pus drained.

On August 17, 1934, **(3)** the child had what were described as two convulsions along with slight fever. No cause was found. At this time laboratory findings were as follows: The blood calcium content was 11.8, and the blood phosphorus level was 4.5. The spinal fluid was under increased pressure; 3 cells; globulin negative; sugar, 60.8; colloidal gold curve, 112332100.

On October 2, 1934, the convulsions recurred, **(4)** and again the child was admitted to the hospital for a few days. Findings were as before including spinal fluid findings and colloidal gold curve, 1123210000. No symptoms were noted, and she was again sent home apparently well.

On November 1, 1934, **(8)** the child was readmitted to the hospital with a fever of 104°F. During the month at home the abdomen, which always on previous occasions had been rather scaphoid, had become distended and gave a doughy resistance on palpation. There were no complaints, but the temperature chart over a period of one month showed a drop to normal in the morning and an evening rise to about 104°F. each day. A diagnosis of tuberculous peritonitis was made. The child became progressively weaker and more emaciated; death occurred on February 11, 1935. **(5)** The duration of her illness from the onset of phlyctenular conjunctivitis was seven years.

Case 2: P. R. (sister of S. M. R., case 1), Negro girl aged thirteen years, was admitted to the Children's Hospital May 7, 1929, complaining of pains in ankles and shoulders. She died June 1, 1934. **(7)**

Present illness: The patient had been apparently in good health until November, 1928 (six months before admission to the hospital), when she began to complain of pain in the ankles. These became swollen from time to time, particularly in the evening after walking. Later the knees and shoulders also became painful. There was a frequent nonproductive cough. Epistaxis occurred about twice a week. There was a slight shortness of breath on exertion, and child complained of being tired. The mother had not "taken any particular notice of lumps in her neck."

There was no change in her general condition until the middle of May, 1934, **(6)** when she became listless. Because of severe headache she was brought to the hospital on May 31 and died the following day. **(7)** Spinal fluid was clear, with 240 cells predominantly lymphocytes, albumin and globulin one-plus. Many acid-fast bacilli were found in the web which formed on standing.

Autopsy was not permitted, but the undertaker was allowed to remove the spleen and one kidney. These he unfortunately put promptly into preserving fluid so that, when they finally arrived at the hospital, animal inoculation was not possible.

When we examine the Buffalo, New York meteorogram (figure 2) of the time indicated in the record, we observe that the first clinical event **(1)**, namely, the death of the father, took place at a time when an unusually sharp polar episode was evident. At about the same time **(6)**, the second daughter became ill; presumably the onset of her meningitis is to be dated to this same period.

In case 1 the date of March 16, 1933 **(2)** is designated as the time whenactivation occurred in the left elbow. This period was one of unusually severe strain, evident on inspection of the meteorogram, where violent barometric fluctuations will be observed. A sharp fall in environmental temperatures had reached its maximum on the 10th of the month and another drop was evident in Buffalo at the time of activation.

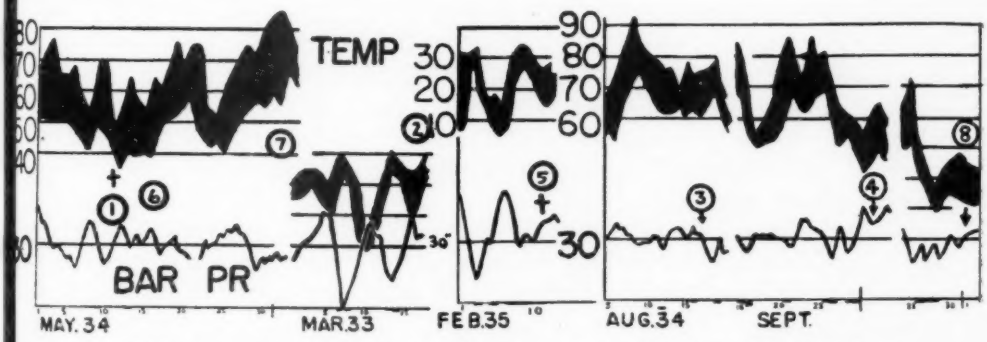


FIG. 2. Meteorogram to illustrate the clinical events in the cases of Dr. Jacobsen.

The convulsions **(3)** occurred with declining temperatures after precipitation and a recurrence of convulsions **(4)** was observed to follow immediately after a sharp barometric crest on the 1st of October, 1934.

When the child was readmitted to the hospital **(8)** on November 1, 1934, it will be noted that a major fall in temperature had occurred during the preceding week and that barometric pressures had been increasing progressively.

Death of the child **(5)** occurred when an environmental situation existed that was quite similar to that observed at the time of the activation **(2)**. In the final episode to be observed, namely, the death of the second daughter **(7)** it will be noted that this was coincident with a minor rise in barometric pressure but occurred at a time when environmental temperatures had increased very rapidly to a fastigium. Such an increase in temperature usually results in marked lowering of blood pressure levels and, with this, deficient return of blood to the heart and an associated vascular stasis.

It will be recalled that this patient was admitted on May 7, 1929; at that time a polar episode had pushed barometric levels up more than one inch in the course of a week. The child was carefully observed and the change in her status **(6)**

which occurred in the middle of May has been discussed in connection with episode **(1)** (the death of the father).

I have made use of this record of Jacobsen's for the simple reason that episodes **(1)** and **(6)**, which occurred during the mid-May cold wave (the death of the father **(1)** and the activation of the tuberculous process in the daughter **(6)** have been discussed in detail in a preceding paper (1). There it was demonstrated not only that activation occurred in patients 3 and 4 but it was also possible to demonstrate the fact that with this cold wave the pH levels were unusually low (page 404) and that capillary permeability was increased, as indicated by increased protein concentration.

FOCAL REACTIONS

In the final analysis we here deal merely with a focal reaction. Just as *any focus* of diseased or dysfunctioning tissue may react to the injection of tuberculin, to a vaccine injection, to physical or mental trauma, to the biological tide of menstruation, to the diurnal cycle—so an impact such as that represented by weather change may initiate a reaction in a purely nonspecific fashion. *So, too, any tuberculous area may react* (in varying degree, depending on its activity or quiescence, on its lability or degree of protection) to tuberculin, to vaccines, to physical or mental trauma, to weather change—with the added implication, however, of the release of bacteria or tuberculo-toxic substances with the initiation of a train of specific events.

I should like to make this perfectly clear, and to do so I make use of another record of Greengard and Hoffman (4), dealing this time with clinical episodes in cases of nontuberculous pericarditis. These simulated acute conditions in the abdomen. The case record is as follows:

Case 1: History: N. M., a white boy, aged nine, was admitted to the children's surgical ward of Cook County Hospital on *November 15, 1928,* **(3)** complaining of pain in the abdomen of four days' duration. **(2)** He had had a sore throat and headache for two days prior to the onset. **(1)** The pain was first noted in the region of the umbilicus, and after several hours shifted to the right lower quadrant and the right lumbar region. Nausea was present at the onset, and vomiting occurred once after the administration of a cathartic. Loose stools were present for three days prior to admission.

Examination: Physical examination of the chest gave negative results, except for roughening of the first sound at the apex of the heart. There was generalized tenderness over the entire abdomen, most marked over the entire right side. Slight rigidity was noted over both upper quadrants, most marked on the right. Peristaltic sounds were present. The child appeared acutely ill, with a temperature of 102.4°F. and a leucocytosis of 23,000. Urinalysis was negative. A diagnosis of acute appendicitis was made and a laparotomy done. The appendix was grossly and microscopically normal, and no peritoneal involvement was present.

Course: Following operation, the boy had a continuous fever of from 101° to 102°F. On the fifth day postoperatively, he complained of pain in the knees. **(4)** The joints were swollen, hot and tender, and acute rheumatic fever was diagnosed. On the seventh day, postoperatively, cardiac findings were noted, **(5)** consisting of enlargement, palpable thrill, systolic and diastolic murmur and a loud friction rub over the entire pre-

cordium. At this time the boy gave a history of repeated attacks of severe rheumatism. A diagnosis of rheumatic fever with pancarditis was made, and the child was transferred to the medical service. The course was protracted, with several recurrences of fever, pain in the joints, precordial pain and pain in the neck. On August 17, 1929, the patient was finally discharged with a diagnosis of chronic endocarditis with mitral stenosis and insufficiency and aortic regurgitation.

When we examine the meteorogram (figure 3) in connection with this case report, it will be observed that the onset **(1)** occurred with the passage of a polar air mass and with a barometric crest. At this time he had a sore throat and headache. Such symptoms follow the increase in blood pressure that is commonly associated with the passage of a colder air mass and merely make evident tissue swelling (perivascular, in the brain) and the passage of bacteria when the

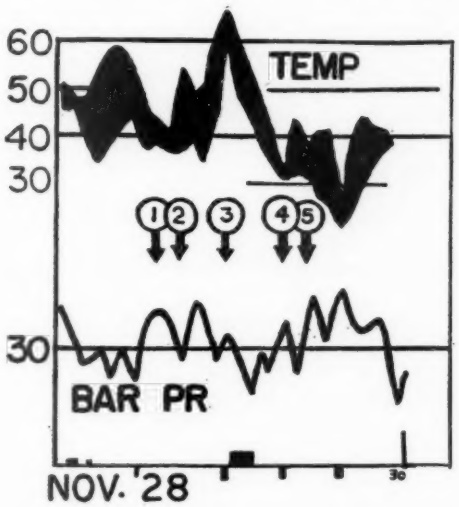


FIG. 3. Meteorogram to illustrate the clinical events in case 1 of Drs. Greengard and Hoffman.

mucous membranes of the throat offer less resistance to invasion after a period of relative anoxia.

Then with the development of a characteristic overcompensation, associated with sudden increase in environmental temperature and fall in barometric pressure, pain in the abdomen began **(2)**.

He was admitted to the hospital **(3)** at a temperature crest. It was a period of considerable meteorological disturbance made evident by severe precipitation on the following two days.

The postoperative pain in the knees **(4)** occurred with the crest of a polar air mass (relative anoxia about the joints followed by swelling) and finally the development of cardiac findings **(5)** occurred with the next succeeding passage of a cold air mass, that is, each frontal passage added a greater cardiac load and this became evident in the clinical picture.

Case 2: History: C. S., a colored boy, aged twelve, was admitted to the surgical service on June 13, 1929, **(2)** complaining of pain in the right side, headache and pain in the right knee of six days' duration. **(1)** The onset was abrupt, with sharp stabbing pain in the epigastric region. Shortly afterward, the pain shifted to the right lower quadrant, where it remained constantly, though on one occasion it radiated down both thighs. The child had never had a similar attack previously. Nausea was present but no vomiting. Pain in the right knee had been present during the entire week, and was severe enough to confine the patient to bed. He had had about five of these attacks during the past three years, usually lasting about one month. The bowel movements were normal during the entire course.

Examination: The boy appeared subacutely ill and in considerable pain. The results of examinations of the heart and lungs were entirely negative. There was tenderness in both lower quadrants of the abdomen, especially on the right, with slight rigidity over the right rectus muscle. Peristaltic sounds were audible. On rectal examination,

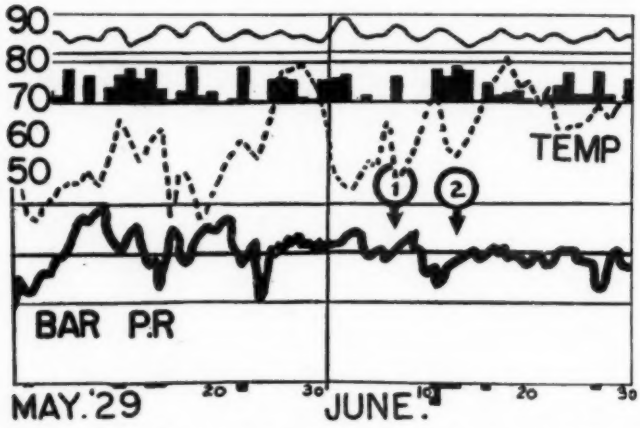


FIG. 4. Meteorogram to illustrate the clinical events in case 2 of Drs. Greengard and Hoffman.

tenderness was noted in the right lower quadrant. The right knee was painful with much muscular spasm.

Course: A diagnosis of appendicitis was made, and an appendectomy was done. The appendix was grossly and microscopically normal. Postoperatively, the boy had a continuous fever, the temperature being as high as 103°F. On the second day, a pericardial friction rub was heard, and a diagnosis of rheumatic pericarditis was made. The course was stormy, with high fever and considerable cardiac embarrassment showing evidence of patchy consolidation in the fields of both lungs at one time. The patient was finally discharged from the hospital on July 23, with a diagnosis of chronic endocarditis with mitral insufficiency.

When we examine the meteorogram[3] (figure 4) we note that pain in the right side of the belly, headache and pain in the right knee **(1)** began with the passage of a polar air mass which had occurred secondarily after a period of unusually

[3] In the meteorograms 4 and 5 the uppermost curve indicates wind velocity, black columns the relative cloudiness, and the dotted line the daily mean temperature.

warm weather at the end of May. Hospitalization (2) on June 13 occurred with the passage of the next cold air mass. During this and the preceding two days there had been marked precipitation.

Case 3: F. J., a colored boy, aged thirteen, was admitted to the surgical service on September 4, 1931 (3) complaining of abdominal pain of two days' duration (2). Three days prior to admission, he had had a headache and pain in the neck (1). The following morning he noted a diffuse pain in the epigastrium. In a few hours, the pain shifted to the right lower quadrant, where it persisted as a dull ache. There was no associated nausea or vomiting and the bowel movements were normal.

Examination: The child did not appear acutely ill or in pain. The temperature on admission was 99.8°F. A systolic murmur was present at the apex and transmitted to the axilla. There was moderate tenderness in the right lower quadrant of the abdomen just to the right of the navel with no muscular rigidity. There was slight rebound

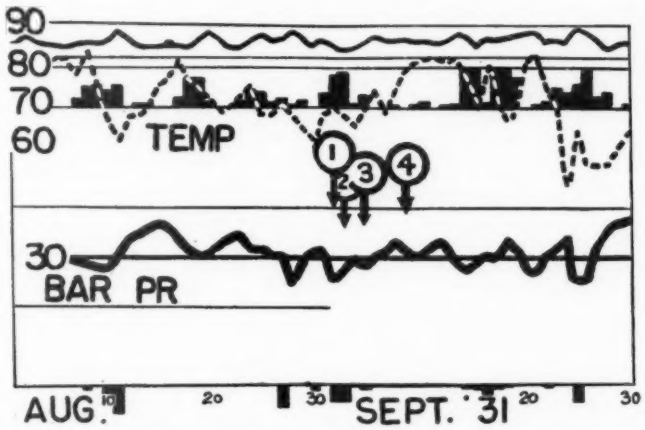


FIG. 5. Meteorogram to illustrate the clinical events in case 3 of Drs. Greengard and Hoffman.

tenderness, and peristaltic sounds were present. The leucocyte count was 22,000, the urine was negative.

Course: A diagnosis of appendicitis was made, and an appendectomy done. Pathologically, the appendix was normal grossly and microscopically. There was no apparent peritoneal involvement at laparotomy. Postoperatively the child had a constant temperature around 101°F. On the fourth day, he complained of pain in the left side of the chest, and a definite pericardiac friction rub was heard. He was transferred to the medical service with a diagnosis of rheumatic pericarditis. The course was uneventful and he was discharged on October 9, in good condition. On several occasions, he complained of precordial pain and pain in the right side of the neck.

When we examine the meteorogram (figure 5) of this period of observation, we note the characteristic trend of events: headache and pain in the neck immediately in the wake of the polar crest (barometric pressure highest on the 31st) and, with this, relative anoxia of tissues, either associated or preceding the onset of the headache. Severe meteorological disturbance (indicated by maximal pre-

cipitation) then followed, and abdominal pain **(2)** began with the beginning passage of the next polar air mass. Admission to the hospital followed **(3)** with the next atmospheric interface. The postoperative complication, pain in the left side of the chest, occurred immediately in the wake of the next barometric crest.

Of importance as we scan the weather of the time is the general association of the precipitation of clinical episodes with the temperature trough. This particular human organism was able to adjust to the environment until too great a strain was placed on the adjusting mechanisms by the maximal development of the mid-summer cold wave.

DISCUSSION

The case records here presented have been selected at random from the literature to illustrate the fact that, when clinical episodes are carefully dated, it is frequently possible to associate the changes in the clinical picture with changes in the meteorological environment in which the patient exists. These meteoropathological interrelations are not specific for tuberculosis, they can be observed in every patient and this for the simple reason that the human organism is constantly pendulating in a biological rhythm that is largely conditioned by the atmosphere, though obviously every change in environmental conditions, no matter what their origin, will in some degree require adjustment and to this degree influence a labile focus, whether tuberculous in origin or not.

Observations such as these are not new—indeed they go back to the Hippocratic texts—and they are so obvious that they require no complicated statistical analysis, but they so counter current physiological teaching that the last paper of Lawrence Henderson's was devoted to the fallacy of the physiologist who predicates the deductions drawn from animal experiments with the assumption of "all other things being equal." All other things are not equal! There is no static base line. The environmental situation is never repeated for any individual organism that exists in an unstable atmosphere such as ours. Consequently each patient must be studied individually. It is only when we consistently analyze the clinical picture from this point of view that we can begin to clarify the seemingly bizarre and conflicting symptom-pictures presented by our patients.

At first glance the realization of the extremely labile status of a patient that reacts as a weather vane, that pendulates like a delicately balanced scale and oscillates with every cosmic force, seems most confusing and discouraging. Actually when once this pendulation of a state of increased resistance and decreased resistance, of decreasing and increasing hydration, of increasing or lessening pH levels, of calcium ionization, of lipoid levels, of leucocytic maturation, of capillary permeability, of pressor levels, etc. becomes common clinical property, the evaluation of the clinical picture, the management of the patient and the prognosis should, I think, be materially facilitated.

The major factors in swinging the organic balance are evident; they are the diurnal cycle, the seasonal cycle, the uncertain and constantly changing atmospheric cycle, the long climatic cycle. The sex cycles of the individual (adoles-

cence and the menstrual cycle), the periodic change in gastrointestinal function, the seasonal cycles in the character of food, the cycles of physical activity (occupations, sports, etc.), all these and many other forces must be considered. In their essence they all merely swing the organic state between two poles, one of which is of benefit, the other of harm to the tuberculous focus (see also the paper of R. S. Wimpenny in the Quarterly Review of Biology 1941, *16*, 389).

SUMMARY

A series of case records are analyzed and the association of the precipitation of clinical symptomatology to the meteorological situation of the time is made evident. A discussion of organic polarity with pendulation of the human status between two poles is presented and the significance of this pendulation for a labile, tuberculous focus is discussed.

SUMARIO

Analízase una serie de protocolos clínicos, poniéndose de manifiesto la asociación de la precipitación de la semiología clínica con la situación meteorológica para la misma fecha. Preséntase una discusión de la polaridad orgánica con la pendulación del estado humano entre dos polos, y discútese el significado de esa pendulación en relación con un foco tuberculoso lábil.

REFERENCES

(1) Petersen, W. F., Howe, J. S., and Milliken, M. E.: Weather and resistance in pulmonary tuberculosis, Am. Rev. Tuberc., 1941, *44*, 377.
(2) Blatt, M. L., and Greengard, J.: Pericarditis as a primary clinical manifestation of tuberculosis in childhood, Am. J. Dis. Child., 1928, *35*, 631.
(3) Jacobsen, A. W.: Generalized tuberculosis of the lymph nodes and multiple cystic tuberculosis of the bones, J. Pediat., 1936, *8*, 292.
(4) Greengard, J., and Hoffman, S. J.: Pericarditis simulating an acute condition of the abdomen, Arch. Surg., 1933, *26*, 623.
(5) Henderson, L. J.: The study of man, Science, 1941, *94*, 1.

HAEMORRHAGIC-NECROTIC REACTION TO TUBERCULIN PPD[1]

Shwartzman or Arthus Phenomenon?

ERICH URBACH AND HAROLD L. GOLDBURGH

We are reporting a case of tuberculous lymphadenitis in which 0,000,002 mg. of Tuberculin Purified Protein Derivative (PPD) injected intracutaneously was followed by a severe haemorrhagic-necrotic local reaction and systemic manifestations (septic fever, thrombocytopenia). This is to be considered not as the type of severe tuberculin reaction occasionally seen in tuberculous patients, but an expression of hypersensitiveness, which corresponds both clinically and histologically, to the Shwartzman phenomenon. Since these manifestations could be elicited only by tuberculin—and not by streptococcus vaccine—the possibility of a specific anaphylactic reaction, the Arthus phenomenon, must be taken into consideration.

CASE REPORT

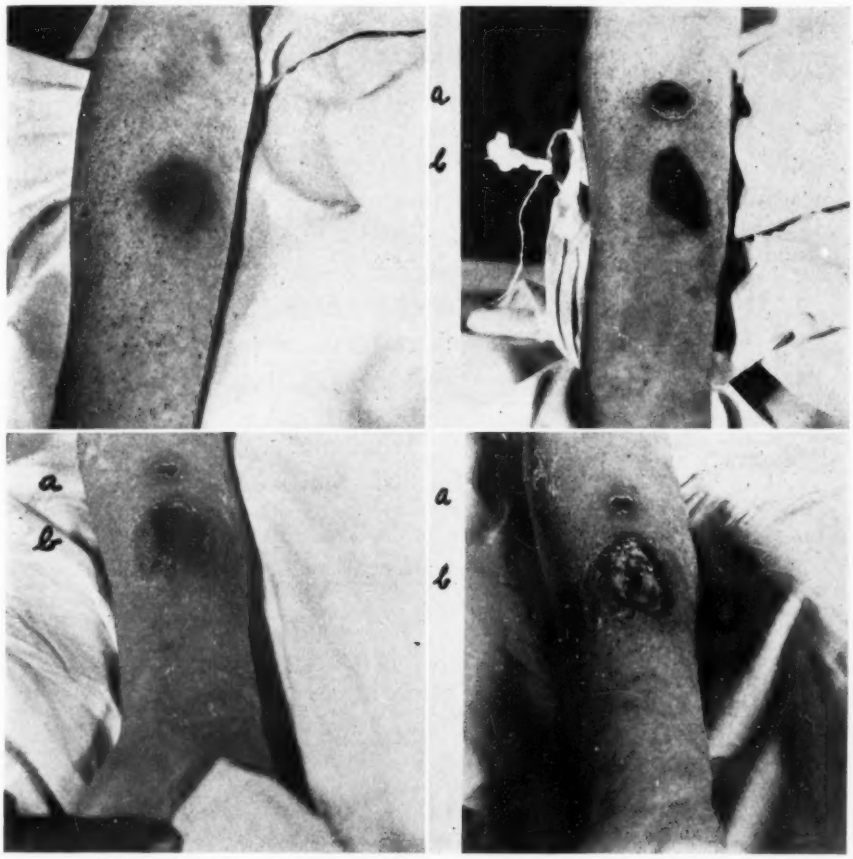
G. McK., age fifty-one, was admitted to the Jewish Hospital on August 6, 1941 with symptoms of cardiac decompensation. Her past medical history revealed that at the age of fourteen years enlargement of the superficial lymph nodes appeared. In 1919 she attended the Out-Patient Skin Clinic of the Massachusetts General Hospital at which time a diagnosis of erythema induratum (Bazin) with lymphadenitis was made. In earlier life and again in 1935 she had attacks of recurrent epistaxis. During one of these episodes she was admitted to the Jewish Hospital and evidence of rheumatic heart disease was discovered. In May, 1940 she noticed that the lymph nodes in the left supraclavicular and both axillary areas were becoming larger. Under X-ray therapy, the nodes decreased in size but did not disappear entirely.

Upon admission, the patient was cyanotic and moderately dyspnoeic. The heart was enlarged in all diameters and double aortic and mitral murmurs were present. The electrocardiogram indicated moderate myocardial damage. The X-ray film of the chest revealed enlargement of the heart and dilatation of the aorta; the lung fields showed evidences of cardio-pneumofibrosis, but no tuberculosis. The liver was enlarged 5 cm. below the costal margin. There was oedema of the lower extremities. The posterior cervical, the left supraclavicular and the axillary nodes were enlarged but not tender or adherent to the skin. The skin of both legs showed numerous punched-out lesions of violet color, due to scars following tuberculids, and one larger scarred lesion, slightly pigmented, suggestive of a healed nodule of erythema induratum (Bazin).

The patient seemed to improve under rest and digitalis. She had an occasional rise in temperature to 99.4°F. in the afternoons. On August 20 the left, supraclavicular nodes enlarged rapidly. A biopsy revealed a chronic tuberculous lymphadenitis with areas of caseous necroses. Eleven days later the first test dose of PPD (0.000,02 mg.) was given intracutaneously in the left forearm. In twenty-four hours, a large angry red indurated area appeared, measuring one inch in diameter. Two days later the whole area became necrotic (figure 1) and was covered by a haemorrhagic bulla, the entire forearm becoming markedly swollen. Thereafter, the necrosis increased in depth

[1] From the Jewish Hospital, Medical Service of Dr. Harold L. Goldburgh and Allergy Service of Dr. Erich Urbach, Philadelphia, Pennsylvania.

(figure 2) and was very slow in healing, as can be seen under "a" in figures 2, 3 and 4. One week later, one-tenth of the original dose (0.000,002 mg.) of PPD was given, followed by a reaction of the same haemorrhagic nature (figure 2b), later a deep necrosis (figure 3b), which resulted in a large slough after twenty-one days (figure 4b).



Successive stages of the Shwartzman phenomenon produced intracutaneously by tuberculin PPD. "a" in each figure—first test dose (0.000,02 mg. of PPD); "b" in each figure—one-tenth of first test dose (0.000,002 mg. of PPD).

FIG. 1. (Upper left.) After three days. Haemorrhagic necrosis.

FIG. 2. (Upper right.) a: After eight days. Demarcation of necrosis. b: After thirty hours. Haemorrhagic reaction without necrosis.

FIG. 3. (Lower left). a: After twenty-seven days. Note the very slow healing. b: After twenty days. Necrosis before separation of slough.

FIG. 4. (Lower right.) a: After twenty-nine days. b: After twenty-two days. After separation of slough.

The histological examination of the lesion thirty hours after 0.000,002 mg. of PPD under low power, revealed ulceration of the skin surface with complete loss of the epithelium. The latter was replaced by an almost homogeneous mass consisting of fibrin, numerous disintegrated cells with large infiltrations of extravasated red blood cells in

many places (figure 5). Deeper in the cutis there was intense cellular infiltration which was seen under the high power to consist of many foci of monocytic cells (figure 6). The vessels involved were capillaries and venules the walls of which had undergone acute hyalinization and were greatly thickened. Imbedded in these walls were numerous large endothelial cells resulting from intimal hyperplasia. Many of these cells were seen infiltrating into the perivascular areas joining with the monocytes to form thick cellular collars. No eosinophils were noted and polymorphonuclears were entirely confined to the enlarged blood vessels.

In addition to the local manifestations rather severe constitutional reactions occurred twenty-four hours after each tuberculin test. They consisted of malaise and a septic temperature curve (figure 7) reaching 102.6°F. which lasted for a few days, associated with a sharp drop in the platelet count from a previous 380,000 to 110,000.

A Vollmer tuberculin patch on two occasions showed a superficial vesicular-haemorhagic reaction.

FIG. 5

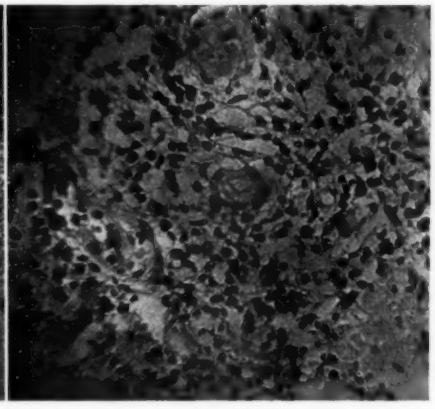


FIG. 6

FIG. 5. Histology of the skin reaction to tuberculin PPD 0.000,002 mg. after thirty hours. Note the haemorrhagic necrosis of the epithelium and cutis to the right, and the infiltration in all layers of the skin. (× 50).

FIG. 6. A high-power view (× 400) of a portion of the subcutis shown in figure 1. The blodd vessel in the centre shows hyalinization, thickening of the wall and a monocytic collar.

The intracutaneous injection of one million organisms of streptococcus viridans vaccine did not produce any reaction.

Passive transfer test with the Prausnitz-Küstner technique was negative on two recipients.

Following the severe local and systemic reactions the patient became toxic, weak and died on October 15, 1941 of cardiocirculatory failure.

Laboratory studies: The urine contained a trace of albumin, many white blood cells and occasional hyaline and granular casts. The P.S.P. test showed an output of 55 per cent within two hours. The blood count was: haemoglobulin 11.6 g. (85 per cent), red blood cells 4,200,000, white blood cells 9,000. Of the latter, 75 per cent were neutrophils and 25 per cent lymphocytes. The blood platelets were 380,000, the bleeding time two and one-half minutes; coagulation time, one and one-half minutes; prothrombin time 75 per cent of average normal. Serological tests for syphilis were negative. The blood chemistry was essentially normal except for a reversal of the albumin-globulin ratio

occurring several days before death. Blood cultures were sterile on three occasions. Serum precipitin titre for tuberculin was found to be 1:20,000 by Dr. F. Seibert of the Henry Phipps Institute.

Autopsy report: An autopsy was performed by Drs. M. Lieber and Norman Schaffer two and one-half hours after death. The external examination revealed a punched-out ulcer on the ventral surface of the right forearm which measured 2.5 by 3.5 cm. and 3 to 4 mm. in depth. There were many depressed scars probably due to tuberculids over

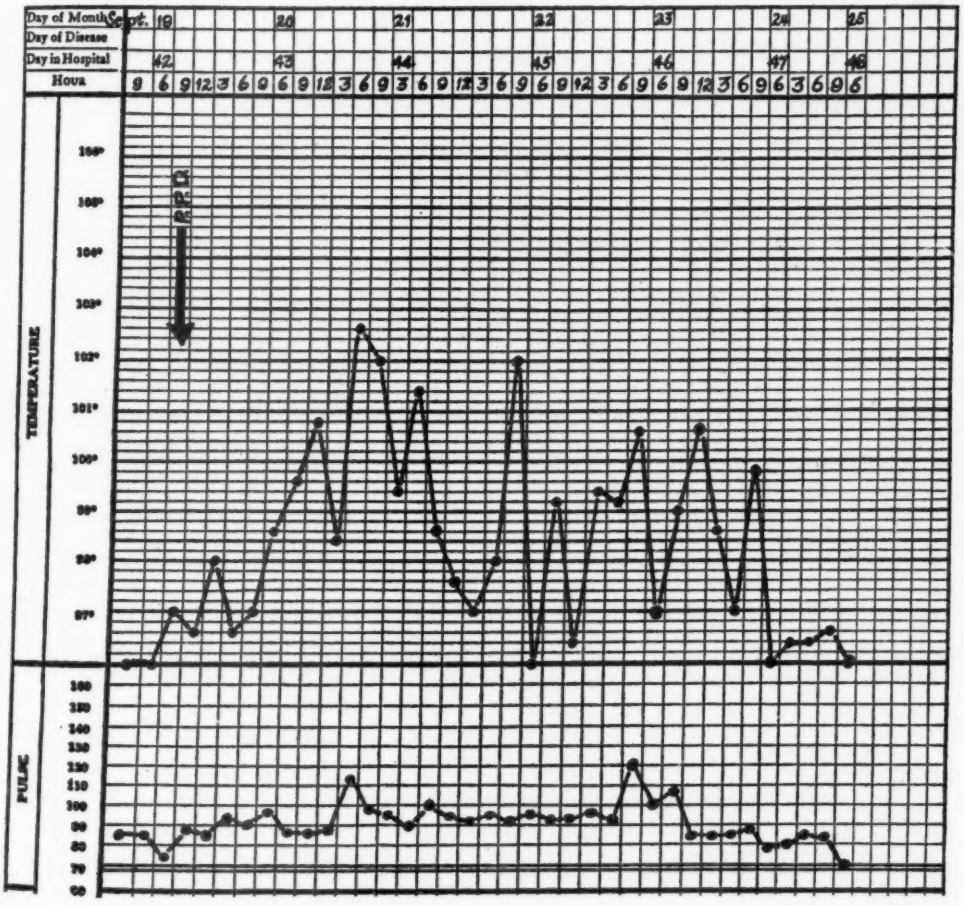


FIG. 7. Temperature curve following the second injection of tuberculin PPD one-tenth first test dose (0.000,002 mg.) showing the septic character of the fever.

the skin of both legs. The peritoneal cavity contained 700 cc. of bloody fluid and there was an enlarged, calcified lymph node in the mesentery. The heart was hypertrophied and dilatated due to chronic rheumatic aortic and mitral valvulitis. The lungs revealed evidences of chronic congestion with a chronic interstitial pneumonitis, but without gross pulmonary tuberculosis. The spleen was enlarged, firm and contained two minute calcified nodes. The stomach was atonic and dilated and the mucosa showed intense congestion with a number of petechial areas. The intestines presented a purple-

velvet appearance with many petechial haemorrhages in the serosa. On sectioning, free blood was present in the lumen. The liver and kidneys were congested. The pelvic organs were normal. The lymph nodes in the neck and axilla were enlarged.

Guinea pig inoculation and culture by the Loewenstein method of the heart blood were negative.[2]

Summary: A fifty-one year old woman with a long history of tuberculosis of the lymph nodes and skin later acquired a heart disease which was considered to be rheumatic. On account of fever in the evening and progressive enlargement of the supraclavicular lymph nodes, one was biopsied and caseous tuberculosis diagnosed. Eleven days later a first test dose of PPD was given intracutaneously, followed within twenty-four hours by a severe haemorrhagic-necrotic reaction and systemic symptoms. One week later a second skin test but with one-tenth of the dose resulted in even stronger local and general manifestations. A Vollmer's tuberculin patch test produced a local vesicular-haemorrhagic reaction. Twenty-six days after the second PPD test the patient died in a toxic state which could not be explained on the basis of the heart disease. Autopsy revealed free blood both in the peritoneal cavity and in the intestines, and diffuse haemorrhages in the wall of the gastrointestinal tract, as well as a calcified node in the mesentery.

SHWARTZMAN VERSUS ARTHUS PHENOMENON

To what extent are the Shwartzman phenomenon and the Arthus phenomenon related? Is it true—as many authorities now claim—that the Arthus phenomenon does not occur in human beings, and that all the severe necrotic-haemorrhagic reactions in human beings are actually Shwartzman phenomena? Is the differentiation between the two of any practical importance?—or is it nothing more than an academic controversy over terminology? In order to have a full understanding of the problem with which we are confronted, it is imperative: (*1*) to have an accurate knowledge of the manifestations of the experimentally induced Arthus and Shwartzman phenomena; (*2*) to analyze the haemorrhagic-necrotic local reactions occurring in human beings and to ascertain whether or not they correspond to the experimental Arthus or Shwartzman phenomena in animals.

By Arthus phenomenon in experimental animals, we mean the intense local reaction, often leading to actual necrosis, which follows the fourth or fifth injection of large doses of foreign sera. These injections need not be given in the same site in order to evoke the characteristic response (Arthus (1)). The tissue-necrosis results primarily from impairment of nutrition, attributable to vascular damage and clogging of the tissue spaces with exudate and haemorrhage. The histological picture of the Arthus phenomenon is characterized by extensive infiltration of the skin and subcutaneous tissues by polymorphonuclear, mononuclear and eosinophilic leucocytes, marked oedema throughout the connective tissue fibres, followed by a degeneration of this tissue to a homogenous mass with

[2] We would like to express our appreciation to Dr. Florence Seibert of the Henry Phipps Institute for her courtesy in doing these studies.

haemorrhages, even in the deeper layers. It is noteworthy that histological evidence of general hypersensitiveness is observed in so-called "local" anaphylaxis. There is a distinct reaction, not only in the regional, but also in other lymph nodes of the body, although to a lesser degree.

Does the Arthus phenomenon occur in human beings? The fact is certainly striking that despite innumerable prophylactic and therapeutic injections of serum that have been given—and in large doses, particularly years ago—there have been very few instances of local manifestations corresponding to the experimental Arthus phenomenon. Search of the literature revealed only the following reports: Lucas and Gay (2), Péhu and Durand (3), Hegler (4), Koehler and Heilmann (5), Gatewood and Baldridge (6), Meleney (7), Tumpeer and Cope (8), Irish and Reynolds (9), Maroney (10), Ross (11), Kohn, McCabe and Brem (12), Brown, Griffitts, Erwin and Dyrenforth (13), Gougerot and Blum (14), Greenbaum (15). In all these reports, except two, severe local necrotic reactions appeared at the site of repeated injections of toxin-antitoxin administered in the course of acute infectious diseases, such as scarlet fever, diphtheria and meningitis. In Brown's (13) case the reactions were due to mosquito bites and in Greenbaum's (15) to repeated injections of histaminase. As will be discussed below, Shwartzman (16), Harkavy and Romanoff (17) and others denied that these were anaphylactic reactions, that is, Arthus phenomena; on the contrary they considered these necrotic processes as an expression of nonspecific local tissue reactivity or Shwartzman phenomenon.

The Shwartzman phenomenon designates the following experimental observations: An animal is prepared by one intracutaneous injection of a bacteria-free filtrate, for example, of typhoid bacillus culture. When the same filtrate is given intravenously twenty-four hours later, a haemorrhagic necrosis occurs at the skin site originally injected, while intracutaneous or subcutaneous reinjection of the filtrate into the original injection-site has no effect. Only those substances can be used for preparing the local skin site, which have the capacity of producing an inflammatory swelling persisting for at least twenty-four hours. Culture-filtrates, containing endotoxins have proved to be particularly suited for this purpose. However, Shwartzman stresses the point that proper skin preparation does not require toxic damage to the tissue, but merely "a functional disturbance in the tissue cells, bringing about a transient state of vulnerability." It is not necessary that the substances employed for preparing the skin and those injected intravenously to provoke the reaction, be identical; nor do they even have to be bacterial filtrates. The phenomenon can be evoked by an intravenous injection of a solution of agar, or of starch, while the skin is prepared by colon bacilli filtrates. The reaction can also be elicited by the intravenous injection of serum precipitates prepared by mixing foreign serum or egg white with homologous antiserum, even when bacterial filtrates were used in the preparatory skin injections. It is also noteworthy that the provoking agents may include not only the precipitates formed in the course of an antigen-antibody reaction *in vitro*, but also the products arising from the union of antigen and antibody *in vivo*. Thus, if a rabbit is sensitized to horse serum, and is given

intracutaneous injections of this serum three weeks later, it will exhibit local allergic reactions. If twenty-four hours later horse serum is injected intravenously, haemorrhages will promptly appear at these sites and will later become necrotic (Albus and Schwarz (18)). As shown by Apitz (19) and confirmed by Horster and Müller (20), a picture corresponding to the Shwartzman phenomenon can be achieved by giving sensitized animals (for example, to horse serum) intracutaneous injections of homologous serum (guinea pig serum) followed twenty-four hours later by an intravenous injection of the same serum. Plaut (21) demonstrated that even partial antigens (haptens) could produce the same results when combined with homologous antiserum. Finally, Bock (22) has shown that the preparation for this reaction can also be achieved by epicutaneous application alone.

According to Gerber (23), the histological changes occurring in the course of the Shwartzman reaction include severe capillary dilatation and engorgement of blood vessels, profuse haemorrhage, venous thrombosis, perivascular collars of leucocytes with infiltration of the vessel walls. The walls of many of the small arteries are hyalinized.

Aside from the symptoms of local tissue reactivity, there is also—as first shown by Sanarelli (24)—a generalized tissue reactivity. This is evidenced, for example, in a severe haemorrhagic diathesis in rabbits receiving intravenous injections, at twenty-four hour intervals, of doses of bacterial filtrates which generally do not produce reactions. Such generalized manifestations in human beings are very rare; a pertinent case following repeated injections of typhoid vaccine will be reported (25). Since this special observation was first observed by Sanarelli, generalized Shwartzman phenomenon is also known as Sanarelli-Shwartzman phenomenon.

To what extent do the necrotic reactions reported in human beings share the characteristics of the Shwartzman phenomenon in animals? Tumpeer and Cope (8) were the first to assume that gangrenous local reactions following serum injections in human beings were examples of the Shwartzman phenomenon. They based this opinion on the fact that the serum of a patient who had been given diphtheria toxin-antitoxin contained certain toxic substances capable of producing the Shwartzman phenomenon in animals: 0.2 cc. of the patient's serum was injected into the skin of a rabbit; twenty-four hours later the animal received 4.5 cc. intravenously and died five hours later with diffuse haemorrhage over the entire abdomen. The authors concluded that the serum must contain bacterial toxin. Kohn *et al.* (12) support this view, pointing out that in the majority of the reported case histories the patient at the time he received the serum injection already had an acute bacterial infection (usually septic sore throat, scarlet fever or diphtheria). They felt that it was logical to assume that there might be an additional factor—a circulating toxin—which produced these violent reactions. Thus, the combined interaction of protein antigen (for example, horse serum) and its antibodies with bacterial toxin at the site of injection might be the cause of the extensive haemorrhage and subsequent gangrene. Harkavy and Romanoff (17) describe three cases with haemorrhagic-necrotic lesions which

appeared following injections of bacterial vaccine or hormone and regarded them as clinical examples of the Shwartzman phenomenon. They concluded that the lesions were produced not merely as the result of repeated injection of a therapeutic serum, but as the product of a series of events consisting of primary serum injections, the presence of circulating toxins and the reintroduction of serum. This sequence conforms with the prerequisites of the Shwartzman phenomenon. The preparatory phase or state of vulnerability in their cases was considered as having been brought about by the circulating toxins derived from the infection which becomes localized in a particular site through the influence of trauma, nonspecific inflammation, etc. The provocative factor is a complex resulting from the union of the serum introduced into the patient and the antibodies produced by the prior introduction of the homologous serum.

The explanation of the pathogenesis of the local haemorrhagic necroses in human beings given by Tumpeer, Kohn, Harkavy and their coworkers coincides perfectly with the corresponding animal experiments of Shwartzman. These workers have shown that when a bacterial filtrate is injected intravenously it may become fixed in sites inflamed by nonspecific irritants or in sites of allergic inflammation. The local factors induce, then, a state of reactivity in these sites. If at this time a protein antigen is injected into an animal sensitized to the same protein, severe damage to these sites results. Finally, there occurs in human beings certain other manifestations which may be interpreted as Shwartzman phenomenon, such as local haemorrhages and even necrosis following acute infections (for example, tonsillitis, influenza, "colds"). They include haemorrhagic and necrotizing appendicitis, pancreatitis, certain types of acute haemorrhagic glomerulonephritis and possibly some cases of haemorrhagic gastritis.

Previous chronic irritation in the organs may be assumed to be the predisposing factor; while the bacterial toxins, entering the blood and lymph streams from the foci of infection may be regarded as the provoking factor. Another equivalent of the generalized form of the Shwartzman phenomenon may perhaps be the sudden haemorrhages into the exanthems in cases of measles and scarlet fever, in the vaccinal area after the first vaccination, in the vaccinal exanthem after revaccination, in anaphylactoid purpuras, etc.

To what extent are we to-day entitled to regard the two forms of local hypersensitiveness, particularly in experimental animals, as basically identical or different? There are two schools of thought. Shwartzman advanced the following reasons for differentiating between the two forms: (*1*) The unspecific local skin reactivity (Shwartzman phenomenon) requires an incubation period of about four to twelve hours and cannot be elicited after a lapse of one hundred and twenty hours, while the incubation period for anaphylaxis is about ten days and the state of sensitiveness lasts for months or even years. (*2*) This local skin reactivity is not specific with regard to the relationship between the preparatory and provocative factor, while anaphylaxis is highly specific. (*3*) The provocative factor for the Shwartzman phenomenon may even be nonantigenic substances, such as agar-agar and starch. (*4*) The Shwartzman phenomenon can be elicited even in an animal rendered anti-anaphylactic by shock. (*5*) The

local skin reactivity cannot be transferred passively by methods which are entirely satisfactory for transferring anaphylaxis passively nor is specific desensitization possible. (*6*) There are clear-cut histological differences between the two phenomena. (*7*) While the Arthus phenomenon is elicited by the subcutaneous route it is essential for the production of the Shwartzman phenomenon that the second dose is given intravenously.

A majority of the investigators who have worked on this problem have come to share Shwartzman's views. Gratia and Linz (26), however, on the basis of their experimental studies hold that the Shwartzman phenomenon is very similar to the Arthus phenomenon and they consider the former to be a variant of the same immunological character although not identical with the Arthus phenomenon.

Apitz (19), Horster and Müller (20), as well as Albus (18) believe that there is a very close relationship between the Arthus phenomenon and that type of Shwartzman phenomenon in which a specific allergic mechanism is operative; that is, those cases in which the same protein is used as both the preparatory and the provocative agents.

Finally we would like to state our own opinion. We hold that the Arthus phenomenon and the Shwartzman phenomenon, both in experimental animals and man, are two different expressions of local hypersensitiveness, the Arthus phenomenon being that of specific hypersensitiveness (that is, allergy) and the Shwartzman phenomenon that of heterospecific hypersensitiveness (that is, metallergy). Stating it in other words, we believe that in the former case there is a specific antigen-antibody reaction, while in the latter there is an altered reactive capacity of a specifically allergized organism to other, or "hetero-antigens." Putting it more concretely, these haemorrhagic-necrotic manifestations depend upon a local hypersensitiveness of the tissue which flares up as the result of the presence of toxic substances or those formed in the course of an antigen-antibody reaction circulating in the blood. (For a detailed discussion of the concept of metallergy the reader is referred to an elaboration of the subject in a paper by one of the present authors (E. U. (27).) We are unwilling to include the Shwartzman phenomenon in the large group of the nonspecific hypersensitivities (nonallergic pathergy) for the reason that it represents a form of hypersensitiveness which may be sharply defined and which follows definite laws; and another reason is that there are certain facts which may be interpreted as evidence of an increased specific tolerance or even of specific immunity. Thus the preparatory or the provocative substance can be neutralized by means of Shwartzman-immune horse serum; moreover, skin can be locally immunized by compresses soaked in culture filtrates so that the Shwartzman phenomenon cannot be elicited (Stohlyhwo (28).)

ARTHUS AND SHWARTZMAN PHENOMENON DUE TO TUBERCULIN

Lewis and Seibert (29) demonstrated in animal experiments that tuberculoprotein is a potent antigen which may be favorably compared with other well-known protein antigens, such as egg-albumin and horse-serum. In 1932, Seibert

(30) reported eliciting typical Arthus phenomena by repeated cutaneous injections of purified undenatured protein of tuberculin. Further purification, however, leading to the preparation of PPD, rendered this tuberculin incapable of sensitizing an animal and therefore incapable of eliciting an Arthus reaction, as well as of producing precipitins and precipitating highly immune serum (Seibert (31)). Seibert never succeeded in producing an Arthus phenomenon with PPD in experimental animals nor has it ever been reported in human beings. While this preparation is in itself unable to call forth antibodies, it can elicit a skin reaction in a sensitized organism; a proof of its hapten nature is offered by the fact that PPD can be rendered antigenic by allowing it to be absorbed on aluminum hydroxide.

There have never been any reports of the elicitation of an Arthus phenomenon by means of the epicutaneous method, not even when stronger antigens than tuberculin were employed. We mention this here, because a Vollmer patch test (epicutaneous application of Old Tuberculin) resulted in a haemorrhagic-necrotic reaction in the patient reported.

Shwartzman (16) carried out a series of investigations in the skin-preparatory and -provocative potency of tuberculin. In addition, heterologous filtrates of ascertained Shwartzman phenomena-producing potency were employed either for skin-preparatory or for intravenous (provocative) injections. When tuberculin OT, diluted 1:7.5, was used for the preparation of the skin, followed twenty-four hours later by intravenous injection of large doses of *M. tuberculosis* filtrates and of tuberculin, no reactions were seen four or twenty-four hours after the intravenous injection. In another series of experiments, the skin of rabbits was prepared by single injections of 0.25 cc. of various batches of human and bovine tuberculin OT and purified TPT the last supplied by Doctor Seibert (Tuberculin TPT is very similar to PPD). Twenty-four hours later the rabbits received single intravenous injections of potent meningococcus and *B. typhosus* filtrates. While some of the batches of tuberculin OT were capable of producing the state of local reactivity, other tuberculins including the purified TPT consistently failed. It is obvious, according to Shwartzman, that the skin preparatory factors in tuberculin occur in low and variable concentrations.

In a third series of experiments by Shwartzman, meningococcus and *B. typhosus* culture filtrates of ascertained skin preparatory potency were employed for intracutaneous injections in rabbits. Various batches of OT were injected intravenously twenty-four hours later. Here again some of the tuberculin preparations were able to elicit severe reactions, while others failed completely.

The results of these experiments clearly show that OT contains the factors necessary for the elicitation of the phenomenon only in low concentrations. Seibert's purified tuberculin TPT, PPD and tuberculin evaporated by boiling over a free flame are negative; while tuberculins prepared by evaporation at 56° C. were able to elicit the phenomenon. Prolonged heating as well as Seibert's purification methods remove the toxic substances which are responsible for the elicitation of the Shwartzman phenomenon.

In this connection the experiments of Freund (32) and Bordet (33) are also

worth mentioning. If tuberculin is injected into the skin of a normal animal, the injection site will, of course, soon regain its normal appearance. If now *B coli* filtrate, for example, is administered intravenously it will not bring on a haemorrhagic reaction. On the other hand, the intravenous injection of *B. coli* filtrate into a tuberculous guinea pig or rabbit, which has responded to an intracutaneous tuberculin injection with local inflammation, will elicit a severe haemorrhagic reaction similar in every respect to the classic Shwartzman phenomenon.

COMMENT

We have presented the case of a woman who for more than twenty years had tuberculosis of the skin and lymph nodes. With the exception of slight scar formation, the skin condition had completely disappeared. But the patient retained a high grade sensitiveness to tuberculin. To what extent the hypersensitiveness is the result or expression of the persisting tuberculous lymphadenitis cannot definitely be decided. But the patient's fever and general physical condition lead to the conclusion that the adenitis far from being terminated was actually progressive. It cannot be denied that the patient's general condition grew worse following the excision of a tuberculous node. It seems as though this procedure had indeed brought on an activation of the specific process, or at least a flooding of the organism with tuberculous toxin.

How then are the haemorrhagic-necrotic reactions following intracutaneous injection of PPD and epicutaneous application of OT to be explained? In view of Seibert's experiments showing the non-antigenic character of PPD, the Arthus phenomenon must be ruled out. Additional arguments against are the onset of septic fever and the drop in platelets. The Shwartzman phenomenon, on the other hand, can be accepted as the explanation in this case because certain conditions were fulfilled. The local inflammatory reaction produced by the interaction of the injected tuberculin with the antibodies in the skin, localized the circulating tuberculous toxin which acted as the provocative principle of the Shwartzman phenomenon; the combined interaction of all these factors (Tuberculin-PPD antigen, its antibodies and the bacterial tuberculous toxin) at the site of injection resulted in the extensive haemorrhage and subsequent gangrene. The accompanying septic fever and the thrombocytopenia indicate the presence not only of a local Shwartzman, but also of a generalized Sanarelli-Shwartzman phenomenon.

However, the question cannot be answered as to why these severe haemorrhagic-necrotic reactions are not observed more frequently following tuberculin skin tests in cases of tubercle bacteraemia.

SUMMARY

1. A patient is reported in whom the administration of 0.000,002 mg. of tuberculin PPD was followed by a severe haemorrhagic-necrotic reaction, accompanied by septic fever and thrombocytopenia. Vollmer's tuberculin patch test produced a local haemorrhagic necrotic reaction, moderate in degree but without systemic manifestations.

On the basis of the clinical course and the histological appearance of the skin reaction, the process is regarded as one of localized Shwartzman phenomenon. However, the unusual autopsy findings (diffuse haemorrhages in the peritoneal cavity, and in the wall and lumen of the gastrointestinal tract) raise the question, whether in addition to the localized Shwartzman phenomenon a delayed generalized Sanarelli-Shwartzman phenomenon was also elicited by the tuberculin injections. If so, since an interval of twenty-six days elapsed between the last PPD injection and death, this would constitute a hitherto undescribed feature; that is, the concomittant occurrence of a localized Shwartzman phenomenon and a generalized Sanarelli-Shwartzman phenomenon.

2. The question is critically discussed as to whether the Arthus and the Shwartzman phenomena are the same or different types of hypersensitiveness.

3. The stand is taken that the Arthus and the Shwartzman phenomena are clinically, histologically and immunologically different expressions of local hypersensitiveness. The Arthus phenomenon is based on a specific antigen-antibody reaction, while the Shwartzman phenomenon is probably a form of metallergy.

4. The majority of cases in human beings that have been described in the literature as exhibiting an Arthus phenomenon actually belong to the group of the Shwartzman phenomenon.

5. The present observations constitute the first reported case of a Shwartzman phenomenon in which: (*a*) the preparatory factor was not a toxin-antitoxin mixture but tuberculin PPD; (*b*) the provocative factor was not reinjected antitoxin serum but bacterial (tuberculous) toxin. It might be speculated that the latter was liberated by the excision of a tuberculous lymph node.

SUMARIO

1. Preséntase un caso en el cual la administración de 0.000,002 mg. de tuberculina PPD fué seguida de una intensa reacción hemorrágico-necrótica, acompañada de fiebre septicémica y trombocitopenia. La prueba del parche de Vollmer produjo una reacción semejante, pero local y moderada, y sin manifestaciones orgánicas.

Tomando por base la evolución clínica y el aspecto histológico de la cutirreacción, considérase el proceso como fenómeno de Shwartzman localizado. Sin embargo, los extraños hallazgos autópsicos (hemorragias difusas en la cavidad peritoneal, y en la pared y luz del aparato gastrointestinal), plantean el problema de si además del fenómeno de Shwartzman localizado la inyección de tuberculina no produjo también un fenómeno generalizado tardío de Sanarelli-Shwartzman. Si es así, como transcurrieron veintiséis días entre la última inyección de PPD y la muerte, esto constituiría una característica no descrita hasta ahora; es decir, concomitancia del fenómeno de Shwartzman localizado y de un fenómeno de Sanarelli-Shwartzman generalizado.

2. Analízase el punto de si los fenómenos de Arthus y de Shwartzman son tipos idénticos o distintos de hipersensibilidad.

3. Tómase la actitud de que los fenómenos de Arthus y de Shwartzman son clínica, histológica e inmunológicamente diversas expresiones de la hipersensi-

bilidad local. El fenómeno de Arthus básase en una reacción específica de antígeno-anticuerpo, mientras que el de Shwartzman es probablemente una forma de metalergia.

4. La mayoría de casos humanos que se han descrito en la literatura como de fenómeno de Arthus pertenecen en realidad al grupo del fenómeno de Shwartzman.

5. Las observaciones actuales constituyen el primer caso comunicado de un fenómeno de Shwartzman en el cual: (*a*) el factor preparatorio no fué una mezcla de toxina-antitoxina, sino tuberculina PPD; (*b*) el factor provocador no fué suero antitóxico reinyectado, sino toxina bacteriana (tuberculosa), cabiendo conjeturar que la última fué puesta en libertad por la excisión de un ganglio linfático tuberculoso.

REFERENCES

(1) Arthus, N.: Injections repetées de serum du cheval chez le lapin, Compt. rend. Soc. de biol., 1903, *55*, 817.

(2) Lucas, W. P., and Gay, F. P.: Localized anaphylactic intoxication in children following the repeated injection of antitoxin, J. Med. Research, 1909, *20*, 251.

(3) Péhu, M., and Durand, P.: Accidents immédiats graves du type anaphylactique, observés au cours des réinjections de sérum antiméningococcique, Lyon méd., 1919, *128*, 303.

(4) Hegler, C.: Hautnekrosen nach wiederholter Injektion von Diphtherieserum, Klin. Wchschr., 1923, *2*, 698.

(5) Koehler, O., and Heilmann, G.: Über vergleichende intrakutane und intravenöse Sensibilisierung des Menschen mit Kaninchenserum, Centralbl. f. Bakt., I. Abt. (Orig.), 1923, *91*, 112.

(6) Gatewood, W. E., and Baldridge, C. W.: Tissue hypersensitiveness following the administration of toxin-antitoxin: Phenomenon of Arthus, J. A. M. A., 1927, *88*, 1068.

(7) Meleney, F. L.: Hemolytic streptococcus gangrene following the administration of scarlet fever antitoxin, Am. J. Surg., 1930, *91*, 287.

(8) Tumpeer, H. J., and Cope, E. J.: The Arthus phenomenon: A serologic study in a syphilitic child with a fatal reaction to transfusion, Am. J. Dis. Child., 1933, *45*, 343.

(9) Irish, H. E., and Reynolds, S. C.: Massive anaphylactic gangrene: Arthus phenomenon, J. A. M. A., 1933, *100*, 490.

(10) Maroney, J. A.: Arthus phenomenon, Report of a clinical case, New England J. Med., 1934, *211*, 106.

(11) Ross, F. E.: The Arthus phenomenon, Report of a case, J. A. M. A., 1934, *103*, 563.

(12) Kohn, J. L., McCabe, E. J., and Brem, J.: Anaphylactic gangrene following administration of horse serum, Arthus or Shwartzman phenomenon, Am. J. Dis. Child., 1938, *55*, 1018.

(13) Brown, A., Griffitts, T. H., Erwin, S., and Dyrenforth, L. Y.: Arthus phenomenon from mosquito bites, South. M. J., 1938, *31*, 590.

(14) Gougerot, H., and Blum, P.: Phénomène d'Arthus nécrotique après une réinjection de sérum antitétanique, Arch. dermato-syph. d'Hôp. St. Louis, 1938, *10*, 67.

(15) Greenbaum, S. S.: Local anaphylactic (Arthus?) phenomena from parenteral injections of histaminase, J. A. M. A., 1940, *115*, 847.

(16) Shwartzman, G.: Phenomenon of local tissue reactivity, 1937, P. B. Hoeber, New York.

(17) Harkavy, J., and Romanoff, A.: Local hemorrhagic-necrotic skin reactions in man (Shwartzman phenomen), J. Allergy, 1939, *10*, 566.

(18) Albus, G., and Schwarz, A.: Ein Beitrag zum Schwartzman Phenomenon, Ztschr. f. Immunitätsforsch. u. exper. Therap., 1938, *93*, 403.

(19) Apitz, K.: Über hämorrhagische Hautreaktionen nach örtlicher Umstimmung, Ztschr. f. d. ges. exper. Med., 1933, *89*, 699.

(20) Horster, H., and Müller, E.: Über die Beeinflussungsmöglichkeiten lokal allergischer, toxischer u. bakterieller Gewebsschäden von der Blutbahn aus, Verhdl. Deutsch. Path. Ges. 30 Tag, 1937, p. 134, Jena, G. Fischer.

(21) Plaut, F.: Untersuchungen über das Shwartzmannsche Phänomen, Ztschr. f. Immunitätsforsch. u. exper. Therap., 1934, *83*, 490.

(22) Bock, H.: Experimentelle Untersuchungen über das Shwartzman Phenomenon, Centralbl. f. Bakt., 1932, *125*, 435.

(23) Gerber, J. E.: Morphologic aspects of the local Shwartzman phenomenon, Arch. Pathol., 1936, *21*, 331.

(24) Sanarelli, G.: Les entéropathies microbiemes, Mason, 1926.

(25) Urbach, E., Goldburgh, H. L., and Gottlieb, P. M.: Death following intravenous typhoid vaccine explained on the basis of a generalized Sanarelli-Shwartzman phenomenon, (in press).

(26) Gratia, A., and Linz, R.: Phénomène de Shwartzman et anaphylaxie, Compt. rend. Soc. de biol., 1931, *107*, 236.
Les phénomènes de Sanarelli et de Shwartzman ou l'allergie hémorrhagique, Ann. Inst. Pasteur, 1932, *49*, 131.

(27) Urbach, E.: Heteroallergy: Parallergy and metallergy, Arch. Pediat., 1941, *58*, 780.

(28) Stohlyhwo, N.: Du caractère spécifique de l'immunité locale de la peau, Compt. rend. Soc. de Biol., 1939, *130*, 31.

(29) Lewis, J. H., and Seibert, F. B.: The chemical composition of the active principle of tuberculin. XIII. The anaphylactogenic action of the protein from filtrates of acid fast bacteria, J. Immunol., 1931, *20*, 201.

(30) Seibert, F. B.: Chemical composition of the active principle of tuberculin. XVI. Local cutaneous sensitization (Arthus phenomenon) produced in normal rabbits and guinea pigs by the protein of tuberculin, J. Infect. Dis., 1932, *51*, 383.

(31) Seibert, F. B.: The isolation and properties of the Purified Protein Derivative of Tuberculin, Am. Rev. Tuberc., 1934, *30*, 713.

(32) Freund, J.: Hemorrhages in tuberculous guinea pigs at the site of injection of irritants following intravascular injections of injurious substances (Shwartzman phenomenon), J. Exper. Med., 1934, *60*, 669.

(33) Bordet, P.: Contribution a l'étude de l'allergie, Ann. Inst. Pasteur, 1936, *57*, 357.

PLASMA PROTHROMBIN IN TUBERCULOUS PATIENTS[1,2]

The Effect of Surgical Collapse

J. W. SAVACOOL AND R. J. CHODOFF

In a recent study of the plasma prothrombin in 70 patients with pulmonary tuberculosis, certain definite and fairly constant trends were demonstrated (1). In fact, the plasma prothrombin level appears to be a fairly sensitive index of the activity of pulmonary tuberculosis. For example, when there is active disease with toxaemia, the prothrombin has been found to be markedly lowered. In more chronic cases, even when the pulmonary lesions are wide-spread, there is a less marked hypoprothrombinaemia and it may be normal in patients with very low-grade activity. When the disease has been controlled with artificial pneumothorax, the prothrombin is frequently elevated above the average normal level. Bradshaw has noted that in the course of certain thoracic surgical procedures on patients with nontuberculous conditions, there is at times a tendency toward abnormal bleeding along with a lowered prothrombin level (2). The purpose of the present study is to determine whether there is a relation between this type of bleeding and the lowered prothrombin which occurs in active tuberculosis and to investigate the effects of various factors, such as cyclopropane anaesthesia, infection and the degree of collapse in patients undergoing surgery for pulmonary tuberculosis. The report includes certain related observations which came to light during the course of the investigation. An attempt is made to interpret the findings on the basis of what is known and postulated concerning the physiology of the plasma prothrombin and the effect of collapse therapy in tuberculosis.

MATERIAL STUDIED AND METHOD

Twelve patients who were subjected to thoracoplasty for pulmonary tuberculosis were studied at various times by a modification of the Quick quantitative method for prothrombin determination (3). The method employed consists of recalcification of oxalated plasma in the presence of thromboplastin obtained from rabbit brain. Results are reported in percentage of average normal and a normal variation of 10 per cent is allowed. Of the 12 patients in this series, 3 had tuberculous empyema and one mixed infection enpyema. The remaining 8 had far advanced pulmonary tuberculosis with cavitation; 3 of them had contralateral pneumothorax. Two had contralateral lesions which were considered quiescent. All except one (case 11, table 1) had acid-fast organisms in the sputum at the time of operation. Cyclopropane anaesthesia was employed in all patients. An attempt was made to correlate the prothrombin determinations with changes in the clinical status, operations or surgical complications. Thus

[1] From the Department for Diseases of the Chest, Jefferson Hospital, Philadelphia, Pennsylvania.

[2] A part of the expense for this study was defrayed from a fund in memory of Howard A. Davis.

TABLE 1

PATIENT	DIAGNOSIS	TIME OF DETERMINATION	PLASMA PROTHROMBIN*
			per cent
1. H.L.	Far advanced tuberculosis, left. Right pneumothorax	Day of operation (preoperative)	87
		6 hours postoperative	89
2. M.O.	Left far advanced tuberculosis with tuberculous empyema	Preoperative	95
		6 hours postoperative	100
3. H.Hu.	Left far advanced tuberculosis with tuberculous empyema. Right quiescent	Day of operation (preoperative)	77
		1 day postoperative. Patient died 24 hours later.	45
4. L.S.	Far advanced tuberculosis, right. Left quiescent	Before first stage	92
		4 days postoperative	48
		18 days postoperative	98
		18 days after second stage	74
5. D.I.	Right far advanced tuberculosis. Left pneumothorax	Before second stage	90
		2 days postoperative	56
		8 days postoperative	81
6. C.Ma.	Right moderately advanced tuberculosis with right mixed infection empyema. Left side uninvolved	Before operation started	51
		Day of first stage	46
		6 hours postoperative	46
		2 weeks postoperative	63
7. C.Mo.	Left far advanced tuberculosis. Right quiescent	Between second and third stages	180
		7 days after third stage	74
8. E.T.	Right far advanced tuberculosis. Left side clear	2 days before first stage	68
		1 day postoperative	39
		2 days postoperative	56
		10 days postoperative	83
		3 days after second stage	80
		2 days before third stage	76
		1 day after third stage	44
		13 days after third stage	85
		24 days after fourth stage	84
9. H.Ho.	Right far advanced tuberculosis. Left pneumothorax. (Impairment of liver function shown by hippuric acid test)	Between second and third stages	53
		Day of third stage preoperative	80
		One day postoperative	54
		5 months later	46
		8 months later	48
10 M.P.	Left far advanced tuberculosis. Right quiescent	Before second stage	91
		6 hours postoperative	73
		10 days postoperative. Wound infection	25
		14 days postoperative. Infection clearing	54
		1 month after third stage	64
11. J.M.	Right tuberculous empyema	Before third stage	69
		1 month after last stage	145
12. S.E.	Right far advanced tuberculosis with atelectasis	1 week before operation	49
		2 days postoperative	78

* Percentage of average normal.

several patients had determinations just before induction of anaesthesia and six hours postoperatively to determine the effect of the anaesthesia on the prothrombin. Some were studied at various times postoperatively to determine when the most marked changes occur. When infection or other complications occurred, determinations were frequently repeated.

In addition to these 12 patients, determinations are reported on 10 other patients who had been subjected to various surgical procedures and who had prothrombin levels which are regarded as characteristic for the phase of their disease.

In all patients studied, chest roentgenograms, vital capacity determinations, erthrocyte sedimentation rates, blood urea and sugar, blood counts and the congo red test for amyloid disease had been carried out.

RESULTS

The details of the findings in the 12 principal patients are recorded in table 1. Patients 1 and 2 (table 1) had determinations made just before induction of anaesthesia and six hours postoperatively in order to determine whether any immediate lowering of the prothrombin occurred. It was found that there was no essential change during this period, the 5 per cent difference in one case being considered as within the margin of error. Thus it is suggested that cyclopropane anaesthesia has no immediate effect on the circulating prothrombin and, if the level is near normal preoperatively, any excess bleeding at operation is not attributable to diminished prothrombin.

It has been found that there is a definite diminution of prothrombin on the first or second day following operation. This usually averages 20 to 30 per cent on the second day, but in certain patients, especially when toxaemia is marked, the drop may be greater. Thus case 3 showed a drop from 77 to 45 per cent in twenty-four hours and died in forty-eight hours. Patient 4 showed a drop from 92 to 48 per cent in four days and in eighteen days it had returned to 98 per cent. Following the second stage, the recovery was not so prompt and the clinical improvement was correspondingly delayed, presumably because of lowered resistance. There was only one exception to the postoperative decrease in prothrombin, patient 12 having shown an increase from 49 to 78 per cent. Patient 5 showed a 34 per cent drop two days postoperatively and while her disease was of the chronic fibrotic type, her general condition was none too favorable for major surgery. Her response was somewhat more marked than usual, but eight days later the prothrombin had almost returned to its preoperative level. In general, the early and late postoperative prothrombin levels appeared to parallel the clinical status and course of events.

Patient 8 was studied at various times during her entire surgical course over a period of three and one-half months. In this patient, the maximum postoperative drop took place in twenty-four hours and on the second day recovery of the prothrombin had already begun. The prothrombin reached 83 per cent ten days after the first stage and did not rise above 85 per cent even after the fourth stage.* Presumably a further rise did occur later since the clinical course was very satisfactory and usually in such patients the prothrombin is

above normal following recovery. The findings in this case are consistent with what may be considered as typical for patients undergoing thoracoplasty.

In only one case (patient 9) was there failure of the prothrombin to rise to normal following surgery which effected satisfactory collapse and control of the disease. In this case the prothrombin reached its highest level just before

TABLE 2

Prothrombin determinations on patients in various phases of surgical collapse

PATIENT	ORIGINAL DIAGNOSIS	TIME OF DETERMINATION	PLASMA PROTHROMBIN*
			per cent
1. W.K.	Moderately advanced unilateral	1½ years after successful thoracoplasty. Sputum negative	180
2. E.T.	Far advanced unilateral	2 years after partial thoracoplasty. Very low grade activity	135
3. C.L.	Far advanced unilateral	3 months after successful revision thoracoplasty. Apparent control	145
4. M.H.	Far advanced unilateral	6 months after revision thoracoplasty with apparent control	110
5. B.C.	Far advanced unilateral	6 months after revision thoracoplasty with persisting activity	89
6. E.L.	Far advanced bilateral	Chronic lesions, low grade activity	85
7. A.C.	Moderately advanced unilateral. Tuberculous empyema	3 months after thoracoplasty. Pleurocutaneous fistula 1 year later	81
8. L.F.	Far advanced unilateral. Tuberculous empyema	Between thoracoplasty stages for pleurocutaneous fistula	75
9. G.O.	Far advanced bilateral. Tuberculous empyema	Partial thoracoplasty right. Soon after start of left empyema	59
10. R.P.	Far advanced unilateral	2 weeks after spontaneous pneumothorax with developing empyema	49

* Percentage of average normal.

the third stage when it was 80 per cent. Following completion of the surgical program it remained between 46 and 64 per cent. Because of this unusual finding, the hippuric acid test for liver function was carried out and it showed definite impairment of liver function which would in itself account for the failure of the prothrombin to return to normal. Oral therapy with vitamin K failed to influence the prothrombin, apparently because of the hepatic damage.

The effect of secondary infection and toxaemia is shown by patient 10. In this case instead of the prothrombin rising above the preoperative level within ten days following operation, the low point of 25 per cent was reached on the tenth postoperative day and the patient was very ill with suppuration of the operative wound. Satisfactory drainage of the infected wound was established soon thereafter and as recovery took place with lessened toxaemia, the prothrombin approached the preoperative level. Patient 11 showed a rather prompt rise in prothrombin following the final operative stage for the control of tuberculous empyema. One month after the operation the prothrombin rose from 69 per cent to 145 per cent. Again, this finding was consistent with the clinical result, the patient having practically no remaining pleural fluid and no other evidence of persistent toxaemia.

Table 2 indicates the prothrombin levels which have been found to be characteristic for the various phases and degrees of activity of the tuberculous process in surgical patients. It will be noted that in those with little or no activity following thoracoplasty there is hyperprothrombinaemia. In the patients with empyema, the prothrombin is markedly lowered. The same observations hold with respect to the preoperative prothrombin levels in the patients in table 1.

COMMENT

The postoperative drop in the prothrombin levels is apparently not directly related to the anaesthesia. This is suggested by the fact that cyclopropane does not have nearly as great a toxic effect on the liver as other anaesthetic agents such as chloroform. Furthermore the results show that the drop in prothrombin usually does not occur promptly but rather during the time when the toxaemia is greatest, namely one or two days after the operation. At this time the patients who showed a marked drop in prothrombin had the higest pulse and temperature and leucocytosis. This most likely results from the operative manipulation in the diseased area and increased circulation in the operative field, with so-called autotuberculinization. It has previously been suggested (1) that the toxaemia might have a destructive effect on the circulating prothrombin in addition to interfering with its production in the liver. This still may be a factor, although there is no positive evidence to support the theory. The difficulty in carrying out liver function tests during the immediate postoperative period has prevented this problem from being settled.

The question of the relationship of bleeding at the time of operation to the prothrombin level has been raised. It may be said that excessive operative bleeding does not result from hypoprothrombinaemia because the study shows that no drop in the prothrombin occurs until twelve or twenty-four hours following operation. Recently one of us had the opportunity to observe patients in whom operation was started under continuous spinal anaesthesia and a change to cyclopropane was made. No abnormal bleeding occurred during the early part of the operation but, soon after the anaesthetic was changed, marked oozing especially from muscle tissue occurred. Apparently cyclopropane brings about capillary dilatation which produces the bleeding.

After collapse therapy has proved effective in controlling the pulmonary disease, there is a progressive increase in the prothrombin level which frequently rises well above average normal. This has been noted in pneumothorax which has been present for some time and this study indicates that the same thing occurs in thoracoplasty. If, as the studies of Andrus *et al.* indicate, prothrombin is destroyed in the lungs, a ready explanation for these findings is offered. When the amount of lung tissue is reduced, less destruction occurs and the prothrombin rises above normal.

It has been suggested that vitamin K administration might prevent the bleeding that occurs during thoracoplasty. Since there is no drop in prothrombin during the time the operation is going on, no benefit may be expected from vitamin K, unless the prothrombin is very low before operation. Even then the effect is quite uncertain since the deficiency results chiefly from toxaemia and hepatic damage rather than from insufficient vitamin K. Since these studies have been undertaken, we have observed a number of patients operated on under continuous spinal anaesthesia. In these cases bleeding has been much less than was formerly seen under cyclopropane. It would appear therefore that the bleeding is not due to any coagulation defect but solely to the effect of the anaesthetic upon the tissues and capillaries. The objection may be made that if this alone were true, patients with far advanced tuberculosis should have a high prothrombin. However, this is prevented by the toxaemia in such cases. When the toxic factors are overcome following successful collapse therapy with reduced vital capacity, the prothrombin does increase.

SUMMARY AND CONCLUSIONS

1. Serial prothrombin determinations were carried out on 12 thoracoplasty patients to study the effect of various factors on the prothrombin level. Single determinations are reported on 10 additional surgical patients who show the characteristic changes for the stage and character of their disease.

2. A marked drop in prothrombin occurs one or two days after operation and usually a week or more is required for return to the preoperative level. This usually occurs according to a definite pattern, depending upon the clinical course.

3. Cyclopropane anaesthesia does not immediately bring about a lowered prothrombin level and the delayed drop probably results from factors unrelated to the anaesthesia.

4. There is a late rise in prothrombin following successful collapse therapy.

5. Vitamin K administration has been found to have little effect on the hypoprothrombinaemia in these patients.

SUMARIO Y CONCLUSIONES

1. Lleváronse a cabo determinaciones seriadas de la protrombina en 12 enfermos toracoplastizados, a fin de estudiar el efecto de varios factores sobre el tenor de protrombina. Comunícanse determinaciones aisladas en otros 10 enfermos quirúrgicos que revelan las alteraciones características del período y naturaleza de su dolencia.

2. Al día o los dos días de la operación sobreviene una pronunciada baja de la protrombina, necesitándose por lo general una semana o más para recuperar el nivel preoperatorio. Esto suele conformarse a un patrón bien definido, según la evolución clínica.

3. La anestesia con ciclopropano no hace descender inmediatamente el tenor de protrombina, y la baja tardía probablemente procede de factores que no guardan relación con la anestesia.

4. Después de una colapsoterapia feliz tiene lugar un alza tardía de la protrombina.

5. Se ha observado que la administración de vitamina K ejerce poco efecto sobre la hipoprotrombinemia en estos enfermos.

The suggestions and criticism of Dr. Burgess Gordon are hereby acknowledged.

REFERENCES

(1) Savacool, J. W.: Am. J. M. Sc., 1941, *201*, 830.
(2) Bradshaw, H. H.: Personal communication.
(3) Quick, A. J.: Am. J. Clin. Path., 1940, *10*, 222.

BROMSULPHALEIN LIVER FUNCTION TEST IN PULMONARY TUBERCULOSIS[1]

ALFRED L. KRUGER AND ISADORE E. GERBER

The effect of chronic diseases upon the functional capacity of the liver has been the subject of many investigations. Numerous liver function tests have been studied in an attempt to establish the presence or absence of hepatic damage, particularly because of the paucity of clinical symptoms. The bromsulphalein test has been favored as against other liver function tests as a more significant indicator of early damage (1, 2, 3, 4).

Soffer (5), in a thorough review, pointed out that the bromsulphalein test of of Rosenthal and White (6) was of value chiefly in the presence of diffuse liver damage. It was his opinion that the 5 mg.-dose test would demonstrate evidence of impaired liver function in from 55 to 65 per cent of instances. O'Leary, Green and Rowntree (7), and subsequently Magath (8) favored the use of the 5 mg.-dose test in the belief that the greater burden imposed upon the liver in the excretion of a large amount of dye was a more adequate test of hepatic function. Other investigators (9, 10) have previously employed the 2 mg.-dose test as advocated in the original publications of Rosenthal and White; their findngs were, in the main, inconclusive. It is possible that these conflicting results may be attributed to the inadequacy of the 2 mg.-dose test.

Our studies concern themselves with the use of the 5 mg.-dose test, exclusively, in patients with early, moderate and far advanced pulmonary tuberculosis, as well as with a group of the latter in whom amyloid disease coexisted.

MATERIALS AND METHODS

The test was performed in a manner previously described by Rosenthal and White with this modification: the first specimen was obtained at the end of fifteen minutes and the second specimen at the end of thirty minutes. Dosage was calculated on the basis 5 mg. per kilogram body weight. In all instances blood was withdrawn from the arm opposite the one in which the dye was injected. The blood withdrawn was divided into three portions; one portion was allowed to clot and the others put into a tube containing, respectively, heparin and potassium oxalate. The comparisons between the standards and the fifteen minute and thirty minute specimens were made with all three blood samples. Gerber and Fryczynski (11) found that heparinized plasma was best suited for dye comparisons and showed a much lower incidence of haemolysis than oxalated plasma or serum. For the present purpose an average estimate of the three results was taken as the final dye retention in the blood. Our standards were prepared as follows: 0.1 g. of the dye was dissolved in a litre of distilled water; 10 cc. of normal sodium hydroxide were previously added to bring out the color. This litre solution represented a 100 per cent standard and subsequent dilutions down to 5 per cent were made. The standards were prepared freshly every two weeks, tightly corked and kept in the dark when not in use. The comparisons between the serum or plasma containing the dye and the standard were made in the Hynson, Westcott and Dunning comparator.

[1] From the Laboratory and Medical Division of the Hudson County Tuberculosis Hospital, Dr. B. S. Pollak, Medical Director, Jersey City, New Jersey.

Fifty-nine cases of pulmonary tuberculosis were studied and these were grouped according to the degree of pulmonary involvement, using the classfication of the National Tuberculosis Association.

For the purposes of control, 5 normal persons (nurses), twenty-four to thirty years of age, were used. All of these showed a retention of the dye in the blood at the end of thirty minutes of from 5 to 9 per cent.

RESULTS

Minimal lesions: (Table 1.) There were 12 patients in this group, their ages varying from sixteen to thirty-six years and the duration of their illness from one week to twenty-one months, with an average of eight months. Clinically there were no evidences of impaired liver function. A 10 per cent retention of dye in the blood was found in only one instance. This patient had been ill for twelve months and showed an uncomplicated resolution of her tuberculosis and was recently discharged from the hospital.

Moderately advanced: (Table 1.) There were 14 patients in the group, their ages ranging from sixteen to thirty-seven years and the duration of their illness from two to one hundred and eight months, with an average of twenty-seven months. Clinically, there was no evidence of liver dysfunction. Five patients showed a retention of 10 per cent or more of the dye at the end of thirty minutes. The dye retained ranged from 10 to 25 per cent. In this group the congo red test for amyloid disease was performed in 8 patients with negative results.

Far advanced: (Table 1.) This group consisted of 13 cases of far advanced lesions in whom there was no demonstrable evidence of amyloid disease. Their ages ranged from eighteen to sixty-four years with a duration of illness from eleven to one hundred and twenty months and an average of forty-five months. Clinically there were no symptoms of liver impairment. The congo red test was performed on all patients and was within normal limits. Seven patients of this group showed retention of the bromsulphalein at the end of thirty minutes varying from 10 to 20 per cent.

Far advanced lesions with amyloid disease: (Table 2.) All 20 patients in this group had positive proof of amyloid disease as evidenced by the congo red test and the presence of urinary alterations such as albuminuria, waxy casts, etc. The ages ranged from twenty-one to sixty-two years and the duration of illness from twenty-six to one hundred and twenty months with an average of sixty-one months. Hepatic enlargement was clinically demonstrable in 16, splenomegaly in 2 and nephrotic oedema in 3. Eighteen of this group presented a retention of bromsulphalein in the thirty minute specimen of from 10 to 35 per cent.

COMMENT

There is some controversy as to what constitutes a normal response to the injection of bromsulphalein. Usually the amount of dye retention in the thirty minute specimen is taken as the criterion of the presence or absence of liver damage. Rosenthal and White used the 2 mg.-dose and considered any dye retention at the end of thirty minutes as indicative of liver damage. However,

with the 5 mg.-dose test many observers (12, 3, 5, 7) felt that a retention of dye of less than 10 per cent was within normal limits and considered 10 per cent

TABLE 1

Bromsulphalein tests in pulmonary tuberculosis

NUMBER	AGE	DISEASE STATE	DURATION OF ILLNESS	CONGO RED PER CENT ABSORPTION	BROMSULPHALEIN TEST AVERAGE DYE RETENTION	
					15 minutes	30 minutes
1	36	Minimal	1 week		12	0
2	28	Minimal	15 months	17	10	5
3	16	Minimal	12 months		25	10
4	27	Minimal	4 months		20	5
5	33	Minimal	21 months	17	12	5
6	18	Minimal	2 months	32	10	5
7	26	Minimal	13 months		5	0
8	35	Minimal	6 months		5	0
9	19	Minimal	5 months		5	0
10	36	Minimal	13 months		5	0
11	22	Minimal	4 months		20	9
12	17	Minimal	3 months		30	8
13	20	Moderately advanced	2 months	32	17	10
14	25	Moderately advanced	4 months	26	15	8
15	16	Moderately advanced	13 months	24	17	5
16	20	Moderately advanced	6 months	14	14	5
17	23	Moderately advanced	60 months	34	10	7
18	17	Moderately advanced	3 months	18	5	0
19	16	Moderately advanced	36 months		10	5
20	31	Moderately advanced	32 months		10	3
21	24	Moderately advanced	4 months		13	8
22	37	Moderately advanced	36 months		30	15
23	25	Moderately advanced	13 months		20	10
24	25	Moderately advanced	108 months	42	40	25
25	21	Moderately advanced	19 months		23	12
26	23	Moderately advanced	48 months	24	25	10
27	26	Far advanced	16 months	14	18	5
28	64	Far advanced	17 months	42	23	10
29	20	Far advanced	11 months	0	12	7
30	31	Far advanced	72 months	0	20	10
31	35	Far advanced	32 months	0	20	8
32	30	Far advanced	14 months	0	40	20
33	26	Far advanced	19 months	14	20	9
34	47	Far advanced	84 months	12	40	15
35	30	Far advanced	120 months	21	20	13
36	18	Far advanced	60 months	29	15	5
37	27	Far advanced	21 months	14	15	8
38	31	Far advanced	96 months	14	25	12
39	33	Far advanced	30 months	0	15	12

retention as the borderline. Our normal controls showed a retention of 5 to 9 per cent. In the entire series studied there were 10 borderline cases. Of these,

6 were patients with far advanced and 4 with minimal or moderate pulmonary tuberculosis. This would seem to indicate that one is justified in accepting the borderline figure of 10 per cent as evidence of dye retention, since the trend in the far advanced cases is toward greater dye retention as compared to the less diseased patients.

Experiences similar to ours with bromsulphalein in pulmonary tuberculosis using the 2 mg.-dose test, were reported by Levinson and Siegal (13). They found that 12 of 28 patients showed a retention of 10 per cent or more of the dye. Of their group, 5 had moderately advanced and 7 far advanced tuberculosis

TABLE 2

Bromsulphalein liver function test in far advanced pulmonary tuberculosis with amyloid disease

All patients showed 100 per cent congo red absorption

NUMBER	AGE	DURATION OF ILLNESS	PALPABLE LIVER	PALPABLE SPLEEN	ALBUMINURIA	NEPHROTIC OEDEMA	BROMSULPHALEIN TEST AVERAGE DYE RETENTION	
							15 minutes	30 minutes
		months						
1	28	84	+	0	+	0	18	8
2	21	60	0	0	+	0	18	15
3	24	26	0	0	+	0	30	20
4	38	120	0	0	+	+	60	33
5	61	34	0	0	+	+	20	12
6	29	32	+	0	+	0	30	20
7	31	84	+	0	+	0	20	5
8	39	84	+	0	+	0	35	30
9	35	108	+	0	+	0	30	15
10	37	39	+	0	+	0	35	30
11	26	108	+	+	+	0	10	10
12	21	60	+	+	+	0	30	10
13	47	40	+	0	+	0	45	20
14	25	52	+	0	+	0	25	15
15	19	60	+	0	+	+	23	18
16	39	96	+	0	+	0	45	35
17	42	84	+	0	+	0	15	10
18	62	48	+	0	+	0	30	10
19	32	43	+	0	+	0	45	12
20	43	60	+	0	+	0	40	30

with only one case of amyloid disease. Tiber, Pearlman and Cohen (14), however, also using the 2 mg.-dose test studied 12 patients of advanced tuberculosis with amyloid disease and found a 5 per cent dye retention in only 2 instances. On the basis of this test, they felt that only 2 of the 12 patients presented minor evidence of hepatic dysfunction. All other liver function tests in these patients were within normal limits; however, a number presented macrocytosis which was considered as indicative of some liver derangement.

Confirmation of the presence or absence of liver damage as determined by the bromsulphalein test, with corresponding histological alterations, is not conclusive. Bauman and Orr (4), in an examination of 32 patients, found a dye

retention of 10 per cent or more in all instances in which there was histological evidence of liver damage. Rosenberg and Soskin (12), DeLor and Reinhart (3) obtained similar results. In the experiences of Bauman and Orr, although their patents with positive bromsulphalein tests showed histological evidence of liver disease, 9 additional cases with a negative dye test showed similar evidence. They concluded that a negative dye test in such instances could be explained on the basis of the enormous reserve capacity of the liver and reported, therefore, a 78 per cent positive correlation between the dye test and the anatomical findings. None of our patients was at any time subjected to an operative procedure. There was only one death with autopsy in the entire series. This patient presented amyloid disease of the liver and a significant bromsulphalein dye retention. We are, therefore, unable to correlate our bromsulphalein findings with histological alterations of the liver.

As is evident from a comparison of the various tables, there is an increased incidence of bromsulphalein retention in patients with far advanced tuberculosis. The incidence rises sharply in instances of complicating amyloid disease. This is particularly significant in view of the fact that other liver function tests as reported by Tiber, Pearlman and Cohen (14) are essentially within normal limits in hepatic amyloidosis. In our series, 18 of 20 patients, or 90 per cent, showed a bromsulphalein retention of 10 per cent or over. It is not clear why the presence of amyloid in the liver appears to affect selectively the dye excretory function.

The reduced ability of the liver, in many instances, to excrete bromsulphalein in the absence of amyloid disease is not readily accounted for by the histo-pathological alterations commonly found in these cases. A review of the alterations seen in livers in instances of far advanced pulmonary tuberculosis reveals slight to moderate fat vacuolization of the liver cells, cloudy swelling, mild or moderate round cell infiltration of the periportal connective tissue, and on occasions minimal central lobular degeneration of the cells. In the absence of complications that may lead to other hepatic changes these findings hardly seem sufficient to account for the diminished bromsulphalein excretion by the liver. Similar pathological alterations may be found without concomitant bromsulphalein dye retention.

It appears then, that hepatic function with respect to bromsulphalein dye excretion may be significantly altered without concomitant morphological evidence. This is not remarkable in the light of similar experiences in other disease states, for example, the presence of jaundice in peritonitis, bronchopneumonia, lobar pneumonia, etc. without significant alterations in the liver.

CONCLUSIONS

The ability of the liver to excrete bromsulphalein is significantly diminished in chronic pulmonary tuberculosis according to the 5 mg. per kilogram body weight test. There is some parallel between this diminished capacity for dye excretion and the chronicity of the disease. There are no significant histological alterations of the liver to account for this reduced function, except when complicated by amyloid disease.

CONCLUSIONES

La capacidad del hígado para excretar bromsulfaleína disminuyó en forma significativa en la tuberculosis pulmonar crónica, conforme a la prueba de 5 mg. por kilogramo de peso. Existe cierto paralelismo entre esa disminución de la capacidad para excretar el colorante y la cronicidad del mal. No se observan en el hígado alteraciones histológicas de importancia que expliquen esa hipofunción, salvo cuando existe la complicación de enfermedad amiloidea.

BIBLIOGRAPHY

(1) McDonald, D.: A practical and clinical test for liver reserve, Surg., Gynec. & Obst., 1939, *69*, 70.

(2) Paulson, M.: Practical application of liver function tests, M. Clin. North America, 1941, *25*, 593.

(3) DeLor, C. J., Reinhart, H. L.: An analysis of the hippuric acid, galactose tolerance, bromsulphalein and prothrombin tests in 381 cases, Am. J. Clin. Path., 1940, *10*, 617.

(4) Bauman, L., Orr, L.: Bromsulphalein test: Checked with liver histology, New York State J. Med., 1938, *38*, 1161.

(5) Soffer, L. J.: Present day status of liver function tests, Medicine, 1935, *14*, 185.

(6) Rosenthal, S. M., and White, E. C.: Clinical application of the bromsulphalein test for hepatic function, J. A. M. A., April 11, 1925, *84*, 1112.

(7) O'Leary, P. A., Greene, C. H., Rowntree, L. G.: Diseases of the liver, Arch. Int. Med., 1929, *44*, 155.

(8) Magath, T. B.: The Takata-Ara test of liver function, Am. J. Digest. Dis., 1936, *2*, 713.

(9) Cornell, V. H.: The bromsulphalein hepatic function test, Arch. Int. Med., 1929, *44*, 819.

(10) Mateer, J. G., Baltz, J. I., Marion, D. F., Holland, R. A., Yagle, E. M.: A comparative evaluation of the newer liver function tests, Am. J. Digest. Dis., 1942, *9*, 1.

(11) Gerber, I. E., and Fryczynski, M.: The use of heparinized blood in studies with congo red and bromsulphalein, Am. J. Clin. Path., 1942, *12*, 312.

(12) Rosenberg, D. H., and Soskin, S.: The Azorubin S. test of liver function: An evaluation with a comparative study of the bromsulphalein and hippuric acid tests, Ann. Int. Med., 1940, *13*, 1644.

(13) Levinson, S. A., and Siegal, H. A.: The bromsulphalein test and blood cholesterol in pulmonary tuberculosis, Am. Rev. Tuberc., 1938, *38*, 229.

(14) Tiber, A. M., Pearlman, A. W., and Cohen, S. E.: Hepatic function in patients with amyloidosis, Arch. Int. Med., 1941, *68*, 309.

STATISTICAL DATA

Edited by MARY DEMPSEY

SANATORIUM FACILITIES FOR TUBERCULOUS PATIENTS, BY STATES

The National Tuberculosis Association has just published a revised edition of its *Sanatorium Directory* which covers all facilities—both public and private—for hospital treatment of tuberculous patients in the United States. The number of beds now available in each state has been compared with the number of deaths from tuberculosis in 1940, the last year for which the Census Bureau has issued final figures.

Early in 1942 the number of beds for tuberculous patients in this country totalled 97,726 or 1.62 per death in 1940. Federal hospitals maintained 9,380

TABLE 1

Deaths from tuberculosis, number of beds for tuberculous patients and ratio of beds per annual death, classified by year. United States*

YEAR*	DEATHS FROM TUBERCULOSIS	TOTAL BEDS† FOR TUBERCULOUS PATIENTS		NON-FEDERAL BEDS FOR TUBERCULOUS PATIENTS	
		Number	Ratio per annual death	Number	Ratio per annual death
1942	60,428‡	97,726	1.62‡	88,346	1.46‡
1938	63,735	89,692	1.41	81,330	1.28
1934	71,609	86,917	1.21	75,486	1.05
1931	84,099	80,054	0.95	69,088	0.82
1928	95,050	72,723	0.77	60,403	0.64
1926	101,732	67,270	0.66	55,086	0.54
1923	103,507	62,790	0.61	51,215	0.49
1919	131,884	56,633	0.43	§	§
1916	143,177	38,857	0.27		
1911	149,142	26,360	0.18		
1908	149,287	14,014	0.09		
1904	165,781	9,107	0.05		

* Years shown are those in which sanatorium directories have been published.

† Includes federal beds.

‡ Deaths are listed for 1940 since this is the latest year for which final figures are available.

§ Data are not available prior to 1923.

of these beds and 16,469 beds were provided by private or semi-private sanatoria or general hospitals. Beds provided for tuberculous patients in mental and penal institutions are listed separately in the sanatorium directory, but are not included in the totals shown in this article.

Each succeeding edition of the *Sanatorium Directory* has shown a steady increase in the ratio of beds per death as evidenced by table 1.

Health authorities are in more or less general agreement on the point that states with less than two beds per annual death must be considered substandard so far as sanatorium facilities are concerned. This standard of two or more beds per annual death has been met in just one-third of the states. Therefore, it may

TABLE 2

Deaths from tuberculosis in 1940, number of beds for tuberculous patients in 1942, and ratio of beds per death in 1940, for those states with two or more beds per annual death

STATE	DEATHS FROM TUBERCULOSIS IN 1940	TOTAL BEDS* FOR TUBERCULOUS PATIENTS IN 1942		NON-FEDERAL BEDS FOR TUBERCULOUS PATIENTS IN 1942	
		Number	Ratio per death in 1940	Number	Ratio per death in 1940
Rhode Island	236	783	3.32	783	3.32
Minnesota	756	2,548	3.37	2,380	3.15
Connecticut	597	1,876	3.14	1,876	3.14
North Dakota	124	368	2.97	368	2.97
Colorado	600	2,498	4.16	1,748	2.91
Wisconsin	832	2,583	3.10	2,379	2.86
Michigan	1,767	5,087	2.88	5,043	2.85
District of Columbia†	427	1,207	2.83	1,207	2.83
Massachusetts	1,629	4,373	2.68	4,069	2.50
New Jersey	1,787	4,203	2.35	4,203	2.35
New Hampshire	104	240	2.31	240	2.31
Oregon	297	695	2.34	681	2.29
Maine	253	548	2.17	542	2.14
New York	6,259	14,599	2.33	13,357	2.13
California	3,887	8,925	2.30	7,900	2.03
Delaware	125	250	2.00	250	2.00

* Includes federal beds.

† Since the deaths, as shown, are not corrected for residence the ratio of beds per death is unduly high in the District of Columbia.

TABLE 3

Deaths from tuberculosis in 1940, number of beds for tuberculous patients in 1942, and ratio of beds per death in 1940, for those states with one but less than two beds per annual death

STATE	DEATHS FROM TUBERCULOSIS IN 1940	TOTAL BEDS* FOR TUBERCULOUS PATIENTS IN 1942		NON-FEDERAL BEDS FOR TUBERCULOUS PATIENTS IN 1942	
		Number	Ratio per death in 1940	Number	Ratio per death in 1940
Iowa	435	883	2.03	813	1.87
Washington	707	1,737	2.46	1,061	1.50
Ohio	2,792	4,320	1.55	4,082	1.46
Arkansas	987	1,401	1.42	1,401	1.42
Kansas	448	689	1.54	626	1.40
Pennsylvania	4,213	5,974	1.42	5,881	1.40
West Virginia	876	1,226	1.40	1,226	1.40
Indiana	1,378	1,839	1.33	1,839	1.33
Illinois	3,645	4,874	1.34	4,690	1.29
Missouri	1,704	2,185	1.28	2,178	1.28
Maryland	1,441	1,829	1.27	1,819	1.26
Nebraska	225	280	1.24	280	1.24
Montana	225	272	1.21	272	1.21
Utah	89	106	1.19	106	1.19
Vermont	149	176	1.18	176	1.18
Virginia	1,557	1,770	1.14	1,682	1.08
North Carolina	1,783	2,751	1.54	1,901	1.07
New Mexico	401	1,215	3.03	424	1.06
South Carolina	900	927	1.03	927	1.03
South Dakota	189	358	1.89	192	1.02

* Includes federal beds.

be said that these states maintain relatively adequate facilities for treating tuberculous patients. Because federal beds are not restricted to the care of residents of the state in which they are located, the ratio of non-federal beds per annual death has been chosen as the basis for listing these states in order to show the relative adequacy of sanatorium facilities provided for their residents.

TABLE 4

Deaths from tuberculosis in 1940, number of beds for tuberculous patients in 1942, and ratio of beds per death in 1940, for those states with less than one bed per annual death

STATE	DEATHS FROM TUBERCULOSIS IN 1940	TOTAL BEDS* FOR TUBERCULOUS PATIENTS IN 1942		NON-FEDERAL BEDS FOR TUBERCULOUS PATIENTS IN 1942	
		Number	Ratio per death in 1940	Number	Ratio per death in 1940
Florida	960	884	0.92	878	0.91
Wyoming	42	33	0.79	33	0.79
Arizona	853	1,549	1.82	632	0.74
Louisiana	1,391	1,140	0.82	959	0.69
Georgia	1,530	1,051	0.69	1,039	0.68
Oklahoma	1,126	1,059	0.94	768	0.68
Texas	3,797	2,750	0.72	2,331	0.61
Tennessee	2,184	1,288	0.59	1,279	0.59
Mississippi	1,066	516	0.48	516	0.48
Idaho	95	175	1.84	43	0.45
Kentucky	1,982	1,137	0.57	752	0.38
Alabama	1,499	537	0.36	502	0.33
Nevada	79	12	0.15	12	0.15

* Includes federal beds.

TABLE 5

Deaths from tuberculosis in 1940, number of beds for tuberculous patients in 1942, and ratio of beds per death in 1940, classified by country

COUNTRY	DEATHS FROM TUBERCULOSIS IN 1940	TOTAL BEDS* FOR TUBERCULOUS PATIENTS IN 1942		NON-FEDERAL BEDS FOR TUBERCULOUS PATIENTS IN 1942	
		Number	Ratio per death in 1940	Number	Ratio per death in 1940
Hawaii	257	983	3.82	983	3.82
United States	60,428	97,726	1.62	88,346	1.46
Puerto Rico	4,886	1,536	0.31	1,536	0.31
Alaska	270†	30	0.11†	30	0.11†
Philippine Islands	30,000†	770	0.03†	770	0.03†

* Includes federal beds.
† Estimated.

Three states have achieved a definitely adequate ratio of more than three beds per annual death. They are Rhode Island, Minnesota and Connecticut.

In the 20 states listed below only partially adequate facilities are available, since their ratio of beds per death is more than one but less than two.

TABLE 6

Ratio of non-federal beds in 1942 per death in 1940, increase in number of beds since 1923, and 1940 tuberculosis death rate, classified by state

STATE	RATIO OF NON-FEDERAL BEDS IN 1942 PER DEATH IN 1940	NON-FEDERAL BEDS			1940 TUBERCULOSIS DEATH RATE PER 100,000 POPULATION
		1942	1923	Percentage of increase since 1923	
United States	1.46	88,346	51,215	72.5	45.9
Alabama	0.33	502	104	382.7	52.8
Arizona	0.74	632	469	34.8	170.6
Arkansas	1.42	1,401	236	493.6	50.5
California	2.03	7,900	3,277	141.1	56.2
Colorado	2.91	1,748	1,898	−7.9*	53.3
Connecticut	3.14	1,876	1,225	53.1	34.9
Delaware	2.00	250	90	177.8	46.9
District of Columbia	2.83†	1,207	267	352.1	64.2†
Florida	0.91	878	51	1,621.6	50.5
Georgia	0.68	1,039	330	214.8	48.9
Idaho	0.45	43	—	‡	18.0
Illinois	1.29	4,690	3,148	49.0	46.1
Indiana	1.33	1,839	795	131.3	40.1
Iowa	1.87	813	453	79.5	17.1
Kansas	1.40	626	196	219.4	24.8
Kentucky	0.38	752	452	66.4	69.5
Louisiana	0.69	959	213	350.2	58.7
Maine	2.14	542	475	14.1	29.8
Maryland	1.26	1,819	967	88.1	79.0
Massachusetts	2.50	4,069	3,512	15.9	37.7
Michigan	2.85	5,043	2,136	136.1	33.5
Minnesota	3.15	2,380	1,841	29.3	27.0
Mississippi	0.48	516	481	7.3	48.7
Missouri	1.28	2,178	937	132.4	44.9
Montana	1.21	272	130	109.2	40.1
Nebraska	1.24	280	176	59.1	17.1
Nevada	0.15	12	—	‡	71.3
New Hampshire	2.31	240	215	11.6	21.1
New Jersey	2.35	4,203	1,880	123.6	42.9
New Mexico	1.06	424	830	−48.9*	75.2
New York	2.13	13,357	10,501	27.2	46.3
North Carolina	1.07	1,901	848	124.2	49.8
North Dakota	2.97	368	110	234.5	19.3
Ohio	1.46	4,082	2,155	89.4	40.3
Oklahoma	0.68	768	313	145.4	48.1
Oregon	2.29	681	287	137.3	27.2
Pennsylvania	1.40	5,881	3,809	54.4	42.5
Rhode Island	3.32	783	723	8.3	33.0
South Carolina	1.03	927	209	343.5	47.3

* Represents decrease.

† Since the deaths, as shown, are not corrected for residence, the ratio of beds per death and the death rate are both unduly favorable for the District of Columbia.

‡ Since the state had no beds in 1923, the percentage of increase cannot be computed.

TABLE 6—*Concluded*

STATE	RATIO OF NON-FEDERAL BEDS IN 1942 PER DEATH IN 1940	NON-FEDERAL BEDS			1940 TUBERCULOSIS DEATH RATE PER 100,000 POPULATION
		1942	1923	Percentage of increase in 1923	
South Dakota	1.02	192	96	100.0	29.4
Tennessee	0.59	1,279	572	123.6	74.7
Texas	0.61	2,331	1,470	58.6	59.1
Utah	1.19	106	15	606.7	16.1
Vermont	1.18	176	126	39.7	41.4
Virginia	1.08	1,682	851	97.6	58.0
Washington	1.50	1,061	698	52.0	40.6
West Virginia	1.40	1,226	376	226.1	46.0
Wisconsin	2.86	2,379	1,272	87.0	26.5
Wyoming	0.79	33	—	‡	16.8
Alaska	0.11§	30	¶	¶	368.9
Hawaii	3.82	983	350	180.9	60.7
Puerto Rico	0.31	1,536	190	708.4	261.4
Philippine Islands	0.03§	770	245	214.3	183.4

‡ Since the state had no beds in 1923, the percentage of increase cannot be computed.
§ Estimated.
¶ Data not available.

The remaining 13 states fall far below acceptable standards as to the number of beds available for their tuberculous residents. It will be noted that 10 of these 13 states are located in the South or Southwest where the Negro, Mexican or Indian population presents a special hazard so far as tuberculosis is concerned. Three of these states with completely inadequate facilities for treatment are sparsely settled states of the far west.

No state in the Union provides beds on so adequate a basis as does Hawaii with 3.82 beds per death. The number of beds in Puerto Rico, though completely inadequate to meet the need, has nevertheless increased in recent years. The lack of provision for hospital facilities in Alaska and the Philippine Islands is indeed deplorable.

If each state were to meet the minimum standard which offers adequate provision for hospital treatment of its tuberculous patients, the United States should have 40,176 more beds than it has at present.

On the other hand, one must remember how many factors enter into the problem of tuberculosis control other than the provision of suitable institutional care. To be effective, a community's tuberculosis program must include not only enough hospital beds but, in addition, adequate clinic and nursing facilities as well as a sustained, comprehensive campaign for health education, both in the schools and in the community as a whole. Case-finding procedures are likewise important as are satisfactory arrangements for post-sanatorium care and rehabilitation. Then, too, the composition, characteristics and density of the population, the types of industry, the standards of living and of education are general

TABLE 7

Relative rank of states according to ratio of beds per death, increase in beds since 1923 and 1940 tuberculosis death rate*

STATE	RELATIVE RANK*		
	Ratio of non-federal beds in 1942 per death in 1940	Increase† in non-federal beds since 1923	1940 tuberculosis death rate
Alabama	48	4	37
Arizona	39	37	49
Arkansas	20	3	36
California	15	14	39
Colorado	5	45	38
Connecticut	3	33	16
Delaware	16	12	29
District of Columbia	8‡	5	43‡
Florida	37	1	35
Georgia	42	11	33
Idaho	46	§	5
Illinois	25	35	27
Indiana	24	18	18
Iowa	17	28	4
Kansas	21	10	8
Kentucky	47	29	44
Louisiana	40	6	41
Maine	13	41	13
Maryland	27	26	48
Massachusetts	9	40	17
Michigan	7	16	15
Minnesota	2	38	10
Mississippi	45	44	32
Missouri	26	17	25
Montana	29	22	19
Nebraska	28	30	3
Nevada	49	§	45
New Hampshire	11	42	7
New Jersey	10	21	24
New Mexico	34	46	47
New York	14	39	28
North Carolina	33	19	34
North Dakota	4	8	6
Ohio	19	25	20
Oklahoma	41	13	31
Oregon	12	15	11
Pennsylvania	22	32	23
Rhode Island	1	43	14
South Carolina	35	7	30
South Dakota	36	23	12
Tennessee	44	20	46

* The state with the most favorable record is numbered one and so on.

† Or decrease.

‡ Since the deaths, as shown, are not corrected for residence, the ratio of beds per death and the death rate are both unduly favorable for the District of Columbia.

§ Since the state had no beds in 1923, the percentage of increase cannot be computed.

TABLE 7—(*Continued*)

STATE	RELATIVE RANK		
	Ratio of non-federal beds in 1942 per death in 1940	Increase† in non-federal beds sinde 1923	1940 tuberculosis death rate
Texas	43	31	42
Utah	30	2	1
Vermont	31	36	22
Virginia	32	24	40
Washington	18	34	21
West Virginia	23	9	26
Wisconsin	6	27	9
Wyoming	38	§	2

† Or decrease.

§ Since the state had no beds in 1923, the percentage of increase cannot be computed.

considerations, all of which play a more or less active part in determining a state's death rate from tuberculosis.

In table 6 the ratio of non-federal beds per death in 1940 is compared with the 1940 tuberculosis death rate for each state. So far as an individual state is concerned, it is obviously impossible to depend upon adequate hospital facilities as the sole factor which immediately affects the death rate. Nevertheless, of the 16 states with two or more beds per annual death, 11, or 69 per cent, have death rates well below the average of the country as a whole. On the other hand, below-average death rates were recorded in 1940 for but 2 or 15 per cent of the 13 states with less than one bed per annual death. Some of the states in the latter group have more or less limited economic resources where one expects both high tuberculosis death rates and limited hospital facilities.

Table 6 also compares the number of non-federal beds available in each state in 1942 with the number available in 1923. In the United States as a whole the number of non-federal beds has increased 72.5 per cent during this nineteen-year period.

In some southern states, such as Florida, Arkansas, Alabama, Louisiana, South Carolina, and Georgia, the increase in bed capacity since 1923 has been pronounced, even though none of these states has yet attained an acceptable standard. Curiously enough, the number of beds has declined in 2 states: New Mexico and Colorado. This decrease no doubt reflects the lack of present-day emphasis on favorable climatic conditions as one of the most important factors in the cure of tuberculosis.

Table 7 gives the relative rank of each state with reference to the ratio of beds per death, the increase in the number of beds since 1923, and the 1940 death rate from tuberculosis. The state with the most favorable record in each category is numbered one, the next most favorable is numbered two, and so on.

In recent years the U. S. Census Bureau has from time to time published data showing deaths from various causes by type of institution in which they occurred.

TABLE 8

Percentage of 1939 tuberculosis deaths occurring in specified type of institution, classified by state

STATE	PERCENTAGE OF 1939 TUBERCULOSIS DEATHS OCCURING IN—				
	No institution	General hospital	Specialized hospital*	Mental institution	Other institution†
United States	46.2	24.8	22.2	5.8	1.0
Alabama	80.6	8.5	7.1	2.8	1.0
Arizona	49.6	27.3	22.6	0.5	—
Arkansas	83.0	6.1	7.2	3.0	0.6
California	25.2	53.0	16.5	3.9	1.5
Colorado	33.4	39.5	25.3	1.5	0.3
Connecticut	28.4	24.4	38.7	8.3	0.2
Delaware	52.3	13.5	25.8	5.8	2.6
District of Columbia‡	14.8	78.8	2.6	3.8	—
Florida	49.1	22.7	23.6	2.8	1.7
Georgia	79.9	8.6	6.7	3.8	1.0
Idaho§	52.5	22.2	14.1	10.1	1.0
Illinois	29.3	42.6	20.9	6.4	0.8
Indiana	56.8	16.6	19.8	5.8	1.1
Iowa	42.2	13.2	30.2	12.8	1.6
Kansas	50.5	19.1	20.3	7.2	2.9
Kentucky	79.5	7.1	8.6	4.3	0.6
Louisiana	58.1	31.5	6.5	2.9	1.0
Maine	38.8	11.0	38.4	11.4	0.4
Maryland	34.1	27.8	32.2	5.3	0.5
Massachusetts	21.0	24.2	46.5	7.8	0.5
Michigan	18.9	35.4	37.6	7.5	0.7
Minnesota	15.8	29.3	37.6	17.2	0.1
Mississippi	86.4	2.6	5.6	5.1	0.3
Missouri	49.8	21.4	23.7	3.8	1.3
Montana	46.8	25.0	18.1	3.2	6.9
Nebraska	37.4	30.6	22.8	8.7	0.5
Nevada§	39.0	44.1	13.6	—	3.4
New Hampshire	46.8	18.7	20.9	11.5	2.2
New Jersey	22.3	20.5	48.5	8.5	0.2
New Mexico	53.7	26.2	18.9	0.9	0.2
New York	19.5	38.0	34.1	7.9	0.6
North Carolina	65.9	5.9	22.6	3.9	1.7
North Dakota	42.3	19.7	29.6	7.7	0.7
Ohio	39.5	28.1	23.1	7.5	1.8
Oklahoma	68.7	8.2	17.4	5.1	0.7
Oregon	30.3	23.5	35.0	9.9	1.2
Pennsylvania	41.0	28.5	19.0	9.3	2.3
Rhode Island	27.4	11.3	51.9	9.0	0.4

* Includes tuberculosis sanatoria, maternal and children's hospitals, and other specialized hospitals.

† Includes homes for the aged, orphanages, penitentiaries, etc.

‡ Figures for District of Columbia are distorted by the fact that the principal sanatorium is located outside city limits.

§ Fewer than 100 tuberculosis deaths occurred in this state in 1939.

TABLE 8—(*Continued*)

STATE	PERCENTAGE OF 1939 TUBERCULOSIS DEATHS OCCURRING IN—				
	No institution	General hospital	Specialized hospital*	Mental institution	Other institution†
South Carolina	61.3	8.2	25.3	4.7	0.5
South Dakota	61.1	16.3	15.3	7.4	—
Tennessee	77.2	9.6	10.4	2.1	0.6
Texas	73.8	12.3	10.0	3.4	0.4
Utah§	34.7	62.1	—	2.1	1.1
Vermont	53.3	17.5	21.9	7.3	—
Virginia	68.3	8.5	16.2	4.8	2.2
Washington	26.7	26.1	33.7	11.1	2.4
West Virginia	67.5	10.3	16.3	4.9	1.0
Wisconsin	29.3	25.0	38.8	6.4	0.5
Wyoming§	56.4	18.2	21.8	3.6	—
Puerto Rico	78.3	3.4	17.7	0.4	0.2

* Includes tuberculosis sanatoria, maternal and children's hospitals, and other specialized hospitals.

† Includes homes for the aged, orphanages, penitentiaries, etc.

§ Fewer than 100 tuberculosis deaths occurred in this state in 1939.

TABLE 9

Percentage of tuberculosis deaths occurring in specified type of institution, classified by year

YEAR	NO INSTITUTION	GENERAL HOSPITAL	SPECIALIZED HOSPITAL*	MENTAL HOSPITAL	OTHER INSTITUTION†
1940 (total)	43.4	24.8	24.6	6.1	1.1
White	42.0	24.3	25.8	6.9	1.0
Other races	46.7	26.1	21.9	4.2	1.2
1939	46.2	24.8	22.2	5.8	1.0
1936	52.0	23.6	18.2	5.2	1.0

* Includes tuberculosis sanatoria, maternal and children's hospitals, and other specialized hospitals.

† Includes homes for the aged, orphanages, penitentiaries, etc.

The latest year for which this information is available for individual states is 1939. In that year 46.2 per cent of all tuberculosis deaths in the country occurred in "no institution," the great majority presumably at home.

Only 22.2 per cent of these 1939 tuberculosis deaths took place in specialized hospitals, compared with 24.8 per cent in general hospitals. (A special study of institutional deaths in 1936 indicated that seven-eighths of the tuberculosis deaths in "specialized" hospitals actually occurred in tuberculosis sanatoria.)

In 1939 deaths occurring at home (in "no institution") ranged from 86.4 per cent of all tuberculosis deaths in Mississippi to 15.8 per cent in Minnesota and

even to 14.8 per cent in the District of Columbia which is essentially an urban community. In Rhode Island, the state with the highest ratio of beds per annual death, 51.9 per cent of the 1939 tuberculosis deaths took place in specialized hospitals, largely sanatoria. Not a single death was recorded in a specialized hospital in Utah in 1939, since general hospitals cared for Utah's tuberculous patients at that time.

Of all the 1939 tuberculosis deaths occurring in the country as a whole, 5.8 per cent took place in mental hospitals. Although Minnesota has had a very low tuberculosis death rate year after year, the state in 1939 had by far the highest *proportion* of tuberculosis deaths in mental hospitals, 17.2 per cent being so allocated.

What is the trend with reference to the places where tuberculous patients die? At this time, reports are available for but three years, 1936, 1939 and 1940. A study of these reports indicates that a larger proportion of tuberculous patients died in institutions in 1940 than was the case in 1936. In the latter year 18.2 per cent of the tuberculosis deaths occurred in "specialized" hospitals—primarily sanatoria—whereas four years later 24.6 per cent of the tuberculosis deaths were so recorded.

While the proportion of tuberculosis deaths in general hospitals was somewhat higher than that in specialized hospitals in 1936, the percentages shown for deaths in these two types of institutions were almost identical in 1940.

One interesting finding is the increase in the proportion of tuberculosis deaths which are occurring in mental hospitals. The 1940 report of the Census Bureau, which gives this institutional information only for deaths in the country as a whole, indicates that 6.9 per cent of the deaths of white patients occurred in mental hospitals, compared with 4.2 per cent of the deaths among non-whites.

In general, the proportion of white patients who die in institutions is somewhat higher than that for patients of other races. On the other hand, more non-white persons die in general hospitals and more white patients in specialized hospitals.

BOOKS

J. BURNS AMBERSON, JR.: *Chest X-ray Interpretation. With Special Reference to Tuberculosis. Pp. 48, with 28 roentgenograms, published by the National Tuberculosis Association, New York, 1941, paper, twenty-five cents.*

By BRUCE H. DOUGLAS

This concise manual covering the subject of chest roentgenography, especially as it pertains to tuberculosis of the lungs, prepared by one whose extensive clinical experience and recognized skill entitles him to speak with authority, could be read with profit by every internist and every physician interested in diseases of the chest and particularly tuberculosis. The roentgenologist will find the chapter on the pathogenesis and evolution of tuberculosis of especial value in giving a brief but basic explanation of the nature and development of the lesions he views in the roentgenogram.

The author's thesis that "The physician who is familiar with the clinical features of a case is in the best position to appreciate and apply X-ray findings and, if possible, he should always make his own interpretation or consult with the expert roentgenologist who is doing so" is well supported in the material presented.

There is a simple exposition of the technical phases of the production of X-rays and their use in chest roentgenography. The sections on the appearance of various types of lesions are very well done and are made clearer by a number of well chosen and quite well reproduced illustrative cuts made from actual films.

While the great value of the X-ray examination is stressed in detecting early tuberculosis and other beginning pulmonary lesions, the author has not failed to point out that there are certain limitations to this method of examination which must be appreciated.

In these days when large groups are being examined for military service, for industrial employment or for other reasons, it has become necessary for a number of physicians to familiarize themselves with chest X-ray interpretation. These, as well as many others, will find this manual invaluable.

CARLOS FONSO GANDOLFO AND HUMBERTO R. RUGIERO: *Tuberculosis Pulmonar. Pp. 535, with 68 roentgenograms, Editor Aniceto Lopez, Buenos Aires, 1941, paper.*

By HOWARD B. SHOOKHOFF

The authors present a textbook based on the classification of Bard. In this classification there are five broad groupings, namely, parenchymatous forms, interstitial forms, bronchial forms, postpleuritic forms and forms with indeterminate localization. These groups are subdivided one or more times, so that ultimately about thirty different clinical types of pulmonary tuberculosis result. Each of these clinical pictures is presented in a detailed and expertly descriptive

manner, with the emphasis upon the use of the five senses in the diagnostic approach, but with adequate attention to X-ray pictures with which the work is well illustrated. Taken as a whole, these descriptions present very effectively the panorama of pulmonary tuberculosis with all its lights and shadows.

Therapy is taken up at various appropriate points in the book. Valuable detail is available in the therapeutic sections and the various procedures and manipulations are described in a thoroughgoing and practical manner. For example, the discussion of therapeutic pneumothorax, in addition to minute technical details and a discussion of indications and contraindications, pays attention to expected results, possible complications and the general course which the patient is likely to follow. Similar thoroughness marks the discussion of thoracoplasty. The therapy of cavities is taken up rather completely, except that Monaldi's procedure is but briefly referred to, since it is considered still experimental. The technique of pulmonary lavage is described at some length. Practical aspects of gold therapy are covered. Symptomatic therapy is well covered, including detailed description of the treatment of haemoptysis. Many prescriptions are presented in the therapeutic sections.

The main portion of the work closes with a brief description of haematological and serological tests used in pulmonary tuberculosis. An appendix presents a concise discussion of present-day biological concepts in tuberculosis, including the theory of Ranke and the subject of BCG vaccination.

This work appears well conceived as a text for students and practitioners.

HENRY D. CHADWICK AND ALTON S. POPE: *The Modern Attack on Tuberculosis. Pp. viii + 95, New York, The Commonwealth Fund, 1942, fabrikoid, $1.00.*

By MAX PINNER

It comes almost as a surprise that it should be possible to present on some 80 small pages most, if not all, the information that is essential for public health workers for the organization and maintenance of a practical tuberculosis program. But this small manual presents not only the do's and don't's for practical application, it provides as well the why's and it documents convincingly the key statements. This is a genuine achievement in literary economy, in wise selectivity, in complete mastery of a subject that in its specific aspects has just about emerged from many conflicting trials, opinions and observations of the last two decades.

The "Modern Attack"—a thoroughly justified title—is, one realizes in studying the book, essentially the attack used in Massachusetts. To this, the work of Doctor Chadwick and his associates, both in Massachusetts and in Detroit, has, through many years of patient labor, in great measure helped to create the foundation. The successful results in both these localities are the best possible recommendation for the plans outlined by Doctors Chadwick and Pope.

As it behooves the public health worker, emphasis is placed on that feature of the campaign that is primarily amenable to attack by public health work, that

is, the factor of infection and contact, although other pathogenic factors are duly mentioned, though possibly not quite with the emphasis that modern research seems to warrant.

While the aim of the treatise is a near Utopia—a tuberculosis death rate of 10 in 1980 and "the death knell for the tubercle bacillus by 2000"—the methods recommended are far from utopian. Economic limitations are realistically considered and the plan of tuberculosis work appears to be acceptable to any community with reasonable social awareness. Since this, however, is lacking to an appalling degree in certain black spots in the U.S.A. and since the present historical constellation threatens the continuation of many social achievements, it takes a strong optimism to agree fully with the cheerful prediction of the future. However, this does not alter the fact that the "Modern Attack" is sound, that it should be adopted widely, that—in the present stage of our knowledge—it promises the best possible results with an expenditure that should not be prohibitive for any community. Doctors Chadwick and Pope's book should be on the must-list of every worker in tuberculosis, public health and medical social work.

Chronic Pulmonary Disease in South Wales Coalminers. A. *Report by the Committee on Industrial Pulmonary Disease.* B. *Medical Survey by P. D'Arcy Hart and E. A. Aslett, with contributions by D. Hicks and R. Yates.* C. *Pathological Report by T. H. Belt with assistance from A. A. Ferris. Pp. 222, with many illustrations and tables, London, His Majesty's Stationery Office, 1942, cardboard, 10s. 6d.* (*British Information Services, 30 Rockefeller Plaza, New York, New York, $2.90.*)

By LEROY U. GARDNER

The study was undertaken because the incidence of certified silicosis in the anthracite mines of South Wales between 1931 and 1937 had been more than five times as high as in the rest of South Wales and nearly one hundred times that for the coal miners in the rest of Great Britain. Not all the anthracite mines showed an equally high incidence. Approximately 2,000 colliers from 16 mines and 500 coal "trimmers" (coal loaders at docks from four ports) were examined. To orient the study practically the entire working population at one anthracite mine, 560 underground and surface men, were given X-ray and clinical examinations and then occupational histories were taken. A selected group of them were also given tuberculin tests (two strengths OT) and their lung volumes and subdivisions were measured. The balance of the miners came from 15 other mines producing hard, "steam" and soft coal. On these men only X-ray films and work histories were obtained. A second section of the report deals with the pathology in 42 selected autopsies of anthracite and bituminous coal miners and coal trimmers.

The study constitutes an objective description of X-ray findings, pathology and associated clinical symptoms with no attempt to correlate the conditions of dust exposure. The latter are to be reported in a subsequent publication.

One infers that the clinical authors are inclined to attach considerable importance to environmental factors like humidity and depths of the mines, as free silica content of rock and dust are barely mentioned. This factor will undoubtedly be considered in the later section of the report. Because of the fact (recognized in this country and elsewhere) that the X-ray patterns of the coal miners' lungs do not conform in certain respects to those encountered in classical silicosis, the authors have introduced a new classification. This includes the following categories:

(a) Normal
(b) Reticulation
(c) Nodulation
(d) Coalescent nodulation
(e) Massive shadows
(f) Multiple fluffy shadows
(g and h) Indefinite changes

These changes are illustrated by a series of 31 very fine plates with enlarged details of the basic patterns. The authors make no attempt to diagnose evidence of infection by the X-ray films. The category of "reticulation" is repeatedly discussed and emphasized because it has not been used in any of the published classifications. However, many students in the United States are now using the term to describe the pattern produced by inhaling certain other dusts with or without free silica. Both in the coal miner and trimmer, reticulation represents the basic pulmonary reaction. In the former, continued exposure is apt to lead to consolidation (categories d, e and f), but in trimmers, screen men and others exposed to coal with a minimum of contamination by dusts of other composition, progression is uncommon. Reticulation is not infrequently associated with some degree of respiratory disability. Both its frequence and its degree are less than with consolidation and, although age itself is not necessarily a factor, symptoms from reticulation are more apt to occur in the second half of life.

The stages of consolidation (d to f inclusive) are assumed to be the result of progression of the reticulation because of their increasing frequency with continued exposure. However, the pathological section of the report demonstrates that in practically all cases of conglomeration there is an element of latent tuberculous infection. This finding is in agreement with South African and American experience and it would seem preferable to this reviewer to consider conglomerate lesions as evidence of associated infection. The authors have not done so because they found no case with clinically demonstrable tuberculosis. Incidentally the dust reaction has had no influence upon sensitivity to tuberculin.

For purposes of compensation it is proposed that all the categories be included under the term "pneumoconiosis of coal miners," that "anthraco-silicosis" be continued to apply to the consolidated lesions and that "dust reticulation" be introduced with the hope that further research may determine the causative factor or factors.

This valuable report contains a wealth of detail which will be of great interest to any student of pneumonoconiosis. This review has emphasized only certain viewpoints that are new.

Tuberculosis in Industry. Report of the Symposium held at the Saranac Laboratory for the Study of Tuberculosis, Saranac Lake, New York, June 9–14, 1941. Edited by LEROY U. GARDNER. *Pp. 374, with many tables, charts and illustrations, National Tuberculosis Association, New York, 1942, paper, $3.00.*

By LEOPOLD BRAHDY

Much of this material has been published in various journals. There is more than convenience in having it brought together in one volume: this arrangement gives the reader a broad view so that the separate studies assume cumulative significance.

Two facts are again demonstrated. First, that a high tuberculosis incidence is associated with a low standard of living; second, that free silica dust (from hard rock mines, granite cutting, foundries) causes silicosis, which is a potent factor in producing tuberculosis. Investigations are also presented on lead absorption and intoxication, tobacco dust and fumes, marble (99 per cent carbonates), grain, cement and gypsum dusts, hot work rooms, high humidity, radiant heat and physical fatigue. No evidence was found that tuberculosis morbidity is increased by these hazards. There are others still to be investigated, but this symposium demonstrates that most of the ordinary industrial hazards are not important factors in causing tuberculosis. This negative conclusion ought to prove a valuable contribution. An interesting statistical corroboration is the finding that, among wives of the employees in silicosis-producing dust, tuberculosis morbidity is much lower than that of the exposed employees. Among wives of employees in other industry, tuberculosis morbidity is similar to that of the employees.

This symposium impresses two factors upon the reader—low standard of living and infection. Dr. J. A. Johnson discusses specific dietary deficiencies in substandard environments, but no conclusions are drawn. He raises the question whether a patient's past dietary deficiencies may influence disease development even though he had an adequate diet for some time before the onset of disease. The problem of the time of effective exposure is repeatedly considered. One contributor suggests that among foreign-born workers the higher rate of childhood infections plays a major rôle. Several speakers recognize the importance to their practical control procedures of knowing whether endogenous or superinfections are responsible for clinical disease. Some of the studies incidentally have yielded data which must hereafter be considered in the hoary debate on that subject, but none of the studies was consciously directed toward that problem.

When the symposium turns from aetiology to case-finding and rehabilitation,

the social-economic problem is again to the fore. The worker wants to avoid the possibility of being rejected for employment; he fears unemployment more than disease—and who knows which is worse for him? The employer wants to avoid hiring men with lesions, even if inactive, and is not eager to have lesions discovered after employment because he fears unwarranted liability under occupational disease laws. H. D. Sayer cites cases in which liability has been decided by legalistic splitting of imaginary hairs on the medical question of what is occupational. He proposes that employees who develop tuberculosis in specified occupations be awarded benefits under the occupational disease laws, regardless of whether the occupation was an aetiological factor. The plan may solve some difficulties in a limited part of the population. Doctor Sappington points out that this would not diminish but would probably increase discrimination on the basis of X-ray findings. Doctor Edwards of the New York City Health Department has partly overcome workers' objections to mass surveys by making the findings as confidential as those of a private practitioner. Doctor Sawyer's plant in Rochester, New York has partly met the problem by accepting applicants with stabilized lesions, if clinically negative, by sick pay for employees and by reëmploying ex-patients under medical supervision. Until we have a general solution of the economic problem of the wage-earner with tuberculosis, progress in tuberculosis control in industry and rehabilitation must be handicapped everywhere and in some places remain impossible.

The foundations of an American standard of health for the industrial population is being laid by continued investigations and exchange of practical information on specific health problems by men in such diverse fields as have come together for this symposium.

LEIGH MITCHELL HODGES: *The People against Tuberculosis. The Story of the Christmas Seal. Pp. 54, with many photographs, published by The National Tuberculosis Association, New York, 1942, paper, $1.00.*

By JACK MASUR

The Tuberculosis Christmas Seal Sale has grown to be a mighty force in providing dollars to purchase public health. The National Tuberculosis Association booklet by Mr. Hodges is a dramatic story of the life-saving stamp, offering convincing evidence that 114 million dollars worth of the public's pennies have helped much in reducing the tuberculosis death rate to one-fourth of the 1907 figure.

The seal with the double-barred cross is a financial power which not only carries health education to the entire nation but buys the popular action necessary to "study tuberculosis in all its forms and spread knowledge as to its causes, treatment, and prevention."

The booklet is first-rate material for both the practitioner's desk and waiting room table.

JULIAN HERMAN LEWIS: *The Biology of the Negro. Pp. xvii + 433, with 17 tables, The University of Chicago Press, Chicago, Illinois, 1942, cloth, $5.00.*

By MAX PINNER

Doctor Lewis states in the preface that "No organized treatise on racial pathology" exists in spite of the fact that both medicine and anthropology would surely profit from such a treatise. In going through this book the entire truth of this statement is found fully confirmed in practically every chapter. Even in the apparently more simple subject of physical anthropology, there is much disagreement between different writers not only as to interpretation and significance of certain findings, but even as to measurable and ascertainable facts.

It must be obviously one of the aims of the biology and pathology of races to try to distinguish between racial differences due to genotypic factors that set races apart and those that are caused by environment in the widest sense of the word. This distinction—one is convinced after reading Doctor Lewis' book—has not been established firmly for any phenomenon but a number of anthropometric data and apparently for sickle-cell anaemia. The Negro race, especially the American Negro, is obviously a particularly difficult subject for such studies, because the American Negro and white are not only worlds apart in socio-economic conditions and consequently in behavior pattern, but a significant portion of the American Negroes are in consanguinity much closer to the whites than the absolute color line might indicate. Therefore, apparent racial differences may simply be due to environmental conditions, while apparent racial similarities may be the effect of known or unknown blood-mixture.

The first 100 pages are devoted to demography, anatomy, physiology and biochemistry. The remainder of the book is concerned with diseases as they affect the Negro race, both in North America and in Africa.

In certain diseases, for example tuberculosis, sickle-cell anaemia and malaria, significant differences between the races are obvious; in many others they are indefinite and probably insignificant. With the exception of sickle-cell anaemia, a true genotypically founded difference is not proven without doubt.

The author's discussion on tuberculosis is particularly interesting; the pertinent chapter covers some 50 pages and is a well balanced, critical analysis of the available information. Doctor Lewis inclines here, as in most other instances where mortality and morbidity of the Negro exceed those of the white, to account for it by environmental circumstances alone. It is methodologically, of course, entirely correct to do so and to accept biological differences only when living conditions do not provide a plausible explanation. However, the rejection of biological differences where they might explain an apparent disadvantage of the Negro seems to be done with greater critical vigor than in instances where they are used to clarify an apparently racial advantage of the Negro.

According to the relative relevance of the racial factor, be it genotypic or environmental, the various discussions are by necessity of quite different degrees of interest. In some conditions nothing more is done than to enumerate the existing data, many of which seem *per se* irrelevant and some are obviously

biased. But even so, one might wish that the author had more frequently made critical and summarizing statements, so that the reader could know at one easy glance whether or not a given morbid condition is influenced by race. Without this, one must frequently labor through pages of references in order to find out what the author could have conveyed by saying "Racial differences apparently do not exist in regard to this disease." And—to finish the critical part of this review—the proof-reading might have been more careful or successful. While this book seems particularly free of obvious printing mistakes, some rough spots in expressions might have been polished. The reviewer was under the apparent misconception that in a University Press, even the printer's devil would not let such a statement pass that the second half of anthropology is derived from the nonexistent Greek word *ologia*.

But the occasions for criticism are irrelevant compared with the excellent quality of the work as a whole. Doctor Lewis has digested and prepared for rather effortless consumption an enormous amount of literature. All data are well assembled and, as a rule, critically presented. It is of great value, not only for physicians and anthropologists but many a person in public life, to have so ready access to apparently all information extant on the biology of the Negro. Many biased and superstitious opinions are corrected and, whenever Doctor Lewis states his own opinion, it is fully documented and thoroughly supported by facts. For most readers of the REVIEW the book is well worth having just for its excellent chapter on tuberculosis.

NOBLE PIERCE SHERWOOD: *Immunology. Second Edition. Pp. 639, with 27 illustrations, 7 color plates and 16 tables, St. Louis, The C. V. Mosby Company, 1941, cloth.*

By ERNEST WITEBSKY

The second edition of Sherwood's Immunology contains two additional chapters: one on the reticulo-endothelial system and one on serum reactions. The book is now divided into 28 chapters with an appendix on colloids. Illustrations and color plates make it easier for the student to understand the reactions described. A great wealth of material has been accumulated by Sherwood. It seems doubtful, however, whether the medical student would be able to study the book intelligently unless he is especially interested and trained in basic immunology. In some instances it is difficult for the teacher of immunology to understand certain arrangements of the book. Chapter 15, for instance, on toxins and antitoxins contains references to puerperal sepsis, blood banks, mumps and others. The difficulty in writing a book on immunology consists of the fact that there is almost no discipline in medicine to which immunology is not related. It is, therefore, very difficult for one author to cover the entire heterogeneous field. He will be inclined to omit discussions on subjects in which he, personally, is less interested. In this case the chapter on biological specificity, especially organ specificity, seems to be rather short and somewhat incomplete,

as is the discussion of the nature of the Wassermann reaction. However, Doctor Sherwood's book in the present form, though probably only useful as a reference book for the medical student, constitutes undoubtedly the result of a tremendous effort and thorough study which will be highly respected by those who are earnestly interested in immunology.

NETTA W. WILSON AND S. A. WEISMAN: *Modern Medicine, Its Progress and Opportunities. Pp. 218, George W. Stewart, New York, 1942, cloth, $2.00.*

By LEWIS J. MOORMAN

In this handy volume, with attractive format, the authors have undertaken a difficult task. In one small volume it is not easy to give the lay reader an adequate picture of modern medicine. The difficulties have been augmented by an attempt to give the historical background and to indicate progress with suggestions as to opportunities for careers in various fields of scientific research. Naturally, much has been sacrificed in favor of brevity.

The historical approach is most commendable and in many sections of the text it has been employed with dramatic effect. But to one who reads with a knowledge of the history of medicine and even a meagre understanding of the influence of disease upon the destiny of mankind, it appears that many opportunities to establish the continuity of medical progress have been overlooked. In addition, the well informed reader may wonder if the authors have not failed to adequately show the laborious methods and the untiring efforts which have motivated medical progress. The average layman would have a much better appreciation of the advantages which have accrued through modern medicine if he knew how it is steeped in the life blood of a long line of medical scientists, bent upon the acquisition of truth. In addition to certain omissions, there are a few historical errors. Among these are references to William Withering and William Osler. On page 94 we find the following:

"But since Dr. William Withering in 1785 coaxed or bribed an old country woman of England to sell or give him a secret that she knew, we have possessed a way to prevent dropsy through the use of a powerful drug called 'digitalis,' made from the leaves of a flowering plant, the foxglove."

The following is quoted from Withering's own statement:

"In the year 1775, my opinion was asked concerning a family recipe for the cure of dropsy . . . "

It is true that Withering published his account of the foxglove in 1785, but the remarkable adequacy of his report is due to the fact that he devoted ten years to a careful experimental and clinical study of the action of digitalis before he assumed the responsibility of publication.

On page 11 we find the following:

"After the Armistice we hasten back to America to see, if only for a moment, that great and beloved physician whose name is almost as meaningful in modern

times as that of Hippocrates when the world was young. We find Sir William Osler—who will not long survive the loss of his only son in the war just ended—still chiefly concerned for the welfare of his patients."

At this time Sir William Osler was Regius Professor of Medicine at Oxford University, where he had gone in 1905 after resigning his professorship at Johns Hopkins.

In justification of the task performed, it may be said that the text presents an interesting running story, containing a great store of valuable information about modern medicine, made readily available for the lay reader, the prospective medical student and research worker, also for busy doctors who need a "refresher course" in the general progress of modern medicine.

ROBERT A. KILDUFFE AND MICHAEL DEBAKEY: *The Blood Bank and the Technique and Therapeutics of Transfusions. Pp. 558, with 214 illustrations and 1 color plate, St. Louis, The C. V. Mosby Company, 1942, cloth, $7.50.*

By SAMUEL MELAMED

This is a timely book and fills a definite need. In these critical days the subjects of transfusion, blood-bank and dried plasma are of universal interest. I can recommend the book unqualifiedly. It is well written and reads easily. The bibliography is exhaustive and is one of the fine features of the book.

Since every critic must criticize, I have chosen a few isolated points on which there might be disagreement. On page 57 there is the statement, "In hemorrhage following tonsillectomy, blood transfusion has also been found invaluable in arrest of bleeding." Although DeBakey does quote his experience that secondary sutures occasionally do not work and in these cases transfusion is sometimes followed by inexplicable cessation of the bleeding, I feel that such a statement may leave the wrong impression in the mind of the reader, that is, that blood transfusion has some other function in post-tonsillectomy haemorrhage aside from the real purpose, blood replacement and the prevention and treatment of haemorrhage shock.

On page 78, in discussing transfusions for the treatment of pernicious anaemia when the red blood count is below 1,000,000, emphasis is placed on those authors who have advocated such transfusions. No mention is made that the greater number of haematologists and clinicians are against blood transfusions in this disease under any circumstances.

On page 80, the statement is made that repeated transfusions over a long period of time have produced haemochromatosis. This statement is contrary to most clinical experience.

In discussing the indications and contraindications for blood transfusion, there has been too little emphasis laid on the misuse of blood transfusions. Like every other excellent therapeutic agent, the misuse and overuse of blood transfusion have brought it a measure of disrepute. A few clinical experiences (that all of us have had) would have been in order, to show us when blood transfusions

should never be done. In this category fall those transfusions that some clinicians use as freely as caffeine and adrenalin in the dying patient.

In the discussion of blood collection for blood bank (on page 239) no mention is made of the open method, except obliquely by saying that the closed method is the only proper one. Now there are some excellent blood banks in excellent hospitals that use ordinary Mason jars and the open method of blood collection and have no more post-transfusion reactions than those that use all sorts of fancy, expensive bottles with aluminum and rubber tops that priority rulings have made completely unobtainable.

Finally, there is one really serious objection: on pages 257 and 262 two cards are reproduced which show that "white" blood and "Negro" blood are kept separately for respective recipients. In these days of critical fight for democracy such evidence of un-Americanism is glaringly out of place. Besides there is no scientific support for such differentiation.

However, may I repeat that, aside from these few blemishes, the book must be highly recommended. It is clearly written; covers the material thoroughly; has excellent illustrations and a superb bibliography.

FRITZ SCHIFF AND WILLIAM C. BOYD: *Blood Grouping Technic. Pp. xiv + 248, with 45 figures and 67 tables, 1942, Interscience Publishers, Inc., New York, N. Y., cloth, $5.00.*

By SAMUEL MELAMED

Blood grouping technique is a specialized branch of the science of immunology. Various groups are interested in this special branch. There are those who are interested in it for its own sake; there are the many others who are interested in it for the sake of its practical use. Of the latter we find four groups, that is, medical men (haematologists and criminologists) and biologists (geneticists and anthropologists). This book is essentially a laboratory manual written for all these various groups. However, one gets the feeling that the authors (really the senior author, F. Schiff) are more interested in the biologist's and criminologist's point of view than in that of the haematologist and physician. Certainly the chapters on the anthropological and genetic aspects of the subject are excellent. On the other hand, the discussion of that aspect of the subject that pertains to transfusions is more that of the scientist than of the practical haematologist. The slurring over of the slide technique and the accenting of the test-tube technique is witness to this fact.

Furthermore, there is one serious lack in the book and that is a small historical survey of each subject at the beginning of each chapter. The absence of such material makes the book one that will be used only by technicians and isolated specialists. And that is a pity for, despite the book's faults, its authors have a high reputation in this field and the book covers the ground well.

HARRY L. ALEXANDER: *Synopsis of Allergy. Pp. 246, with 22 illustrations and 29 tables, St. Louis, The C. V. Mosby Company, 1941, leather, $3.50.*

By LAURENCE FARMER

Alexander's unassuming little book gives a good review of the present status of the diagnosis and treatment of allergic diseases. It should prove useful to the practitioner who wishes to obtain information concerning problems of this nature. The treatise, which is written with a very practical slant, contributes little to the problem of allergy from a theoretical point of view.

Brief Comment

Tuberculosis Hospital and Sanatorium Directory. Compiled by the National Tuberculosis Association, New York, June, 1942. Pp. 185, fabrikoid, $1.50. This latest (1942) edition of the Tuberculosis Sanatorium Directory is a complete revision of the previous 1938 edition. All Sanatoria are listed in geographical order with information on bed capacity, administrative or financial control, type of cases admissible, character of medical work done (pneumothorax, surgery, etc.).

Of general interest is the fact that in a four-year interval the total bed capacity has increased by 12 per cent, 89,692 to 97,726 beds, and this gain is entirely due to tax-supported institutions, while private institutions showed a decline of 5 per cent bed capacity.

The information includes not only sanatoria and tuberculosis hospitals in the strict sense of the word, but general and mental hospitals with tuberculosis departments and penal institutions similarly equipped. Briefly, the Directory is a complete guide to all existing facilities for the treatment of tuberculosis.

Books Received

F. DENNETTE ADAMS: Cabot and Adams Physical Diagnosis. Thirteenth Edition. Pp. xv + 888, with 398 figures, The Williams & Wilkins Company, Baltimore, 1942, cloth, $5.00.

CONSTANTINO J. CARVALLO: Memoria que Presenta al Congreso Nacional el Ministro de Salud Publica, Trabajo y Prevision Social. Pp. 313, with Apendice of 283 pp., with numerous tables, Lima, Imp. de la Comand. Gral. de Aer., 1941, paper.

MAX ESPINOZA GALARZA: Colapso Pulmonar Quirúrgico. Pp. 155, with 73 illustrations, Lima, Peru, 1941, paper.

W. C. HUEPER: Occupational Tumors and Allied Diseases. Pp. xxviii + 896, 1942, Charles C. Thomas, Springfield, Illinois, fabrikoid, $8.00.

P. ITURBE, H. DELGADO RIVAS AND R. SOTO MATOS: Investigacion sistematica de la tuberculosis en zonas urbanas, rurales, semi-rurales, industriales petroleras e indigenas en el estado zulia. Pp. 183, with many graphs and tables, Caracas, Litografia del Comercio, 1938, paper.

CHEVALIER JACKSON AND CHEVALIER L. JACKSON: Diseases and Injuries of the Larynx. Pp. xi + 633, with over 200 illustrations including 11 plates in color, New York, The Macmillan Company, 1942, cloth, $8.00.

FRANCISCO J. MENENDEZ AND PEDRO HERNANDEZ GONZALO: Le tuberculosis traqueobronquial. Estado actual del problema. Pp. 47, 1941, Cultural, S. A.—La Habana, paper.

DOROTHY B. NYSWANDER: Solving School Health Problems. Pp. xii + 377, New York, The Commonwealth Fund, 1942, cloth, $2.00.

ERIK VON ROSEN: Studien über die Lungendurchleuchtung in der Tuberkulosebekämpfung. Pp. 245, with 74 illustrations, C. W. K. Gleerup, Lund, 1941, paper.

J. SKLÁDAL: The Pleuro-subpleural Zone. Pp. vii + 103, with 11 plates and 20 drawings, Cambridge: At the University Press; New York: The Macmillan Company, 1942, cloth, $2.75.

CARLOS A. URQUIJO AND MARIO WAISSMANN: El rquitismo en el hijo de tuberculosa. Pp. 98, with 154 figures, El Ateneo, Buenos Aires, 1941, paper.

Directory of Medical Specialists, Certified by American Boards, 1942. Directing Editor, PAUL TITUS. Pp. xvi + 2495, published for the Advisory Board for Medical Specialties, by Columbia University Press, New York, 1942, cloth, $7.00.

Anuario de Epidemiologia y Estadistica Vital Ano 1940. Ministerio de Sanidad y Asistencia Social, Direccion de Salubridad Publica, Division de Epidemiologia y Estadistica Vital. Pp. xvi + 361, with many tables, Caracas, Lit. y Tip. del Comercio, 1941, paper.

Memoria del Primer Congreso Venesolano de la Tuberculosis, Caracas, December 8 to 11, 1938. Pp. 576, with many tables and charts, paper.

War Medicine. A Symposium edited by Winfield Scott Pugh; Associate Editor, Edward Podolsky; Technical Editor, Dagobert D. Runes. Pp. 565, New York, Philosophical Library, 1942, cloth, $7.50.

AMERICAN TRUDEAU SOCIETY

Report of the Committee on Undergraduate Medical Education

Dr. Julius L. Wilson, *Chairman*

Dr. John B. Barnwell — Dr. Horton R. Casparis
Dr. Donald R. King — Dr. C. Howard Marcy
Dr. Sidney J. Shipman

The Committee on Undergraduate Medical Education held one meeting during the past year. This was in Louisville, Kentucky, on November 2, 1941. Committee members present were: Dr. J. L. Wilson, Chairman; Dr. J. B. Barnwell; Dr. Horton R. Casparis; Dr. C. Howard Marcy. Dr. Sidney Shipman was unable to attend. There were also present Dr. C. St. C. Guild, Executive Secretary of the American Trudeau Society; and Dr. B. L. Brock by invitation.

This first meeting of the Committee was devoted largely to a discussion of the best method to improve medical education in the field of tuberculosis. It was concluded that the Committee should divide its work into two successive phases: (*1*) to study the present methods of teaching tuberculosis in medical schools with their varying types of facilities; (*2*) to secure the coöperation of those responsible for this teaching and to work out with them certain standards of teaching for the facilities available.

It was decided that the present methods of teaching could best be studied by visits of the members of the Committee to some of the seventy-seven medical schools in the country. For the present, each member of the Committee was assigned a definite geographical area in which he is to select and visit at least four schools for study with reference to certain specific points which were outlined. For this purpose, the President of the American Trudeau Society was requested to add to the Committee a member from the North Atlantic states. Dr. Donald King has since accepted this appointment. The data thus obtained from deans, professors, key men in tuberculosis teaching and others in a sample of twenty-four medical schools will afford a sounder basis than questionnaires for the Committee's final report and for recommendations to the various deans and to the American Society of Medical Colleges. At least a year will be devoted to the study and analysis of present teaching methods.

Our work has suffered to a certain extent from the entry of the United States into active participation in the war. Doctor King is on active duty in Washington. The other members of the Committee are not only engaged in extra duties, but also share our common feeling that the war effort must take precedence over all matters not related directly to it. Yet we intend to carry on this study both for its immediate value in furnishing a guide to the improvement in teaching of medical officers and for its help in improving the curriculum of medical schools after the war.

AMERICAN TRUDEAU SOCIETY

Report of the Committee on X-ray Apparatus and Technique

Dr. D. O. N. Lindberg, *Chairman*

Dr. Ezra Bridge
Dr. F. Maurice McPhedran
Dr. Gilberto S. Pesquera
Dr. Homer L. Sampson
Dr. S. Reid Warren, Jr.
Dr. William Weidman

One meeting, February 7, 1942, in New York City, was held by the Committee for the year 1941-1942, and was supplemented through correspondence and an exchange of films.

1. *American Trudeau Society Film Library:* Dr. Homer Sampson suggests that the proposed film library take the form of an "album" containing a number of films selected from the files of the membership and illustrative of varying techniques and their effect upon the diagnostic value of the film, to be accompanied by suitable legends correlating the technical and interpretative angles, with a perpetuating plan for revision and renewal annually or biennially. This practical approach to the problem of aiding in the betterment of techniques for chest radiography in general might well supplement the setting of standards, especially in regard to the utilization of density limits as expressed by densitometer readings. The Chairman, Dr. D. O. N. Lindberg, proposes submitting to the National Tuberculosis Association and American Trudeau Society Executive Committees the idea of placing four cuts in the next edition of *Diagnostic Standards*, made from films of the same individual with minor lesions and demonstrating low, medium and high densities with medium contrast and medium density with high contrast (accomplished in the laboratories of the Committee members). The originals of these engravings would be available on loan, as it is generally understood that engraved reproductions of celluloid films are at best not entirely adequate for accurate study.

2. *Improvement of the Conventional Chest Film:* Data on the use of a copper tablet as a technical control, as presented by Dr. William Weidman and Mr. Jean Kieffer, have been considered and accepted as a useful criterion for "total technique," as applying to variations in density and contrast. A master film correlating copper tablet densities with densitometer readings forms a guide for evaluating the density on any given film. The Committee suggests that there are changes brought about by variations of technique, as in the agitation of films in solutions, emphasizing the need for stabilizing the details of radiography if the maximum results are to be obtained.

3. *Research:* Dr. S. Reid Warren, Jr.'s work at the Moore School Laboratory continues on the problem of accurate measurement of X-ray output of apparatus on short exposures.

4. *Film Method Evaluation:* Dr. Ezra Bridge's experience, after filming 50,000 cases by the roentgen-photographic method (4″ x 5″), indicates that 98 to 99 per cent of minimal cases are detected through the use of the 4″ x 5″ film. His

appraisal in regard to roentgen-photography versus other film methods is as follows:

1st choice—14″ x 17″ stereo (celluloid)
2nd choice—4″ x 5″stereo
3rd choice—14″ x 17″ single (celluloid)
4th choice—4″ x 5″ single
5th choice—14″ x 17″ paper
6th choice—35 mm. single

While the films of a study of method evaluations by Eugene P. Pendergrass, M.D., S. Reid Warren, Jr., Sc.D., and D. S. Haagensen, M.S., as presented in a paper at a meeting of the Philadelphia Roentgen Ray Society last October, have not become available for review by the Committee, it may be recorded that thirty-one roentgenologists participating in the appraisal expressed preference for the methods as follows:

1st choice—14″ x 17″ celluloid
2nd choice—14″ x 17″ paper
3rd choice—4″ x 5″ stereo
4th choice—35 mm. stereo

A considerable number, however, rated the 4″ x 5″ stereo second and the 14″ x 17″ paper radiograph third with the 35 mm. stereo definitely falling into fourth place.

5. *Body Section Radiography:* The Committee has completed its study of "Body Section Radiography in Thoracic Diagnoses, Including Technical Considerations," as it is being utilized in the field at this time.

Films of a model, cast from a frozen specimen, demonstrating anatomical landmarks on both conventional and planigraphic films, have been prepared by Dr. Gilberto S. Pesquera. Glass bubble "cavities" placed within the parenchymal areas were located accurately and with clear definition on planigraphic films.

The correlation of high speed chest Bucky films and laminograms has been studied by Dr. F. Maurice McPhedran and presented to the Committee, which agrees with his opinion that body section radiography is an invaluable adjunct in the study of cavitation.

Planigraphic films taken by the Committee members on the "round-robin" patient have been examined and compared. In spite of wide variations in apparatus and technique used, the end results were startlingly similar in density, contrast and detail, and more importantly, in cavity delineation.

The conclusions reached by the Committee with regard to the status of body section radiography in the diagnosis and treatment of pulmonary tuberculosis are as follows:

1: This procedure is an important adjunct in the study of cavitation, but need not be utilized in instances of *proved* cavitation.

2: *The diagnosis of cavitation should usually be substantiated by planigraphic exploration prior to major surgery.*

3: With the interpretation of planigraphic films, overinterpretation of "suggestive" shadows should be avoided, inasmuch as true cavitation appears well defined on planigraphic films of adequate technique.

4: Technically, these films should be within the density and contrast limits prescribed for conventional films, to provide for correlation with the conventional type films.

EXPERIENCE WITH MASS X-RAY EQUIPMENT

A Discussion of Parts of the Preceding Report

HERBERT R. EDWARDS[1]

Dr. D. O. N. Lindberg, reporting at Philadelphia for the Committee on X-ray Apparatus and Technique of the American Trudeau Society, rated the 14″ x 17″ paper as the least desirable method. Warren, Pendergrass and Haagensen rated it as next to the 14″ x 17″ celluloid film in diagnostic accuracy. The report by Warren *et al.* was discussed by advocates of the fluorographic methods but time did not permit further discussion from the floor.

The impression seemed to persist in the minds of many that the paper roentgenogram was not a satisfactory method and should be discarded. Whether this idea was intended or not it seems appropriate to report briefly the experiences in the use and observation of these methods in New York City.

The background from which our conclusions are drawn may be outlined as follows:

1: Since 1933, the Department of Health has used the rapid paper method in mass surveys exceeding 450,000 persons.

2: Since 1933, paper in cut sheets has been used in our routine clinic services in increasing numbers as its quality has been improved.

3: During these years repeated comparisons of 14″ x 17″ paper and celluloid films have been made. Our conclusions have repeatedly indicated that it is possible to detect minimal parenchymal changes as readily on paper as on celluloid in routine work.

4: On several occasions the comparative roentgenograms on 14″ x 17″ celluloid and paper and the fluorographic films of others have been reviewed.

5: Likewise, we have seen a great many of the 35 mm. fluorographs, some made in comparative studies, some by independent investigators, such as D'Abreu, those of the National Surveys, Inc. of New Jersey and the work of Seth Hirsch at Beth Israel Hospital in New York City. The unit of Hirsch was set up in our clinic and 100 chests were radiographed on celluloid, paper and the 35 mm. film. Reading these films independently by several of our staff revealed that over 10 per cent of the lesions were missed on the small film, several of which were minimal lesions in the apex and along the periphery of the lung fields.

For convenience our conclusions can be briefly summarized under six major headings.

1. *Diagnostic Accuracy:* This is the first criterion of any method. As previously indicated, our experience definitely places 14″ x 17″ paper next to 14″ x 17″ celluloid; the 4″ x 5″ next and the 35 mm. film last and on a par with fluoroscopy.

2. *Facility of Operation:* The roll paper method is a mobile unit and can therefore be readily moved from point to point. The roll paper method can operate

[1] Director, Bureau of Tuberculosis, Department of Health, New York, New York.

with facility at 150 exposures per hour, in some instances even faster though this is usually unnecessary.

3. *Facility in Reading:* The roll paper can be read faster and with less eyestrain than either of the fluorographic methods. In our services one team can read up to 2,000 per day, and as a routine 1,000 per day.

Members of our staff fully conversant with the paper and 4″ x 5″ films report that with the latter approximately 75 to 100 films are read per hour, and that they cannot read for more than two hours without eyestrain and fatigue.

4. *Facility in Filing and Storage:* To set up filing equipment for the smaller films will mean new devices and the utilization of two systems so long as 14″ x 17″ celluloid is used. While paper requires more space than celluloid we have overcome it by microfilming on 35 mm. and storage on 100 ft. spools, containing approximately 850 reductions.

5. *Service Factors:* The roll paper method is more flexible on a service basis as it can be brought in when needed, and in our service up to seven units per day have been operated. The use and adjustment of staff to a program varying from one to seven units, as in our experience, would be impossible.

The use of the fluorographic equipment requires capital outlay and maintenance, with personnel for operation.

6. *Cost:* In the roll paper method, cost is based on the unit plan, varying according to the number of films exposed in a specified time. In the fluorographic method, unit cost per film finished will be more than the cost of the film, quoted at one cent for the 35 mm. single and five cents for the 4″ x 5″ with the generally recommended stereoscopic films at double this amount. Initial expense for apparatus and depreciation, especially of the rotating anode tube, raises costs noticeably.

In conclusion, it must be obvious that all methods have some value, dependent upon the job to be done, the type of case, the numbers involved and the availability of the facilities. The roll paper method has best met the requirements of the survey program in the Department of Health, and apparently a number of other users, doing occasional surveys, report the same.

MANAGEMENT OF PATIENTS WITH OCCASIONALLY POSITIVE SPUTUM AFTER APPARENTLY ADEQUATE THERAPY

Clinical Aspects[1]

ARTHUR M. STOKES[2]

While it may not be possible for us to reach an absolute agreement upon the definition of an "occasionally positive sputum" we can all probably agree that the bacillary content of the sputum is an accurate reflection of the dynamic status of pulmonary tuberculosis and the presence of bacilli in the sputum indicates at least some degree of pathological activity. Also it is almost axiomatic that, if the number of bacilli in the sputum is decreasing or remains stationary over relatively long periods of time, the physical activity of the patient may be safely increased. If, on the other hand, the bacillary content tends to increase, further treatment is necessary. Since the ultimate object of therapy is eradication of the disease, any and all means should be used to accomplish this result but failing its achievement the patient must be taught now to live with his disease.

If tubercle bacilli are occasionally found in a patient's sputum every possible diagnostic procedure should be employed to determine their source, appreciating the fact that minimal lesions in adolescents and young adults and so-called round infiltrates not infrequently have very long refractory periods before permanent sputum conversion takes place.

Bronchoscopy: Although it is conceded in general that clinical diagnoses of bronchial tuberculosis are at least as accurate as those made by direct vision, many lesions are so small or so early that they have produced insufficient changes in the bronchial mucosa to cause either subjective or objective signs and yet these lesions can and do shed bacilli and bronchoscopic examination is therefore almost invariably indicated in these problem cases. If a lesion is discovered and it appears amenable to treatment this should be instituted in spite of the fact that, up to the present time, the results of local treatment may be equivocal. For thoroughness, no bronchoscopy can be considered complete without examination with the retrograde lens which permits inspection of the bronchi to the upper lobes where the focus is so often located. Even though no definite lesion can be identified bronchoscopy not infrequently affords valuable clues as to the possible source of bacilli: (*1*) a deviation from the normal salmon-pink color of the mucosa to the redness of inflammatory changes, as determined by comparison with adjacent normal bronchi, is always suspicious and this is especially so if this redness is on the floor or in the most dependent portion of the bronchus, and (*2*) if pus is actually seen coming from a bronchus it should be aspirated and examination may reveal tubercle bacilli. (Parenthetically it is suggested that if the daily amounts of sputum are well nigh negligible it may be helpful to administer mod-

[1] Presented in the Panel Discussion before the Medical Section at the 38th annual meeting of the National Tuberculosis Association, Philadelphia, Pennsylvania, May 6, 1942.

[2] Homer Folks Tuberculosis Hospital, Oneonta, New York.

erately heavy sedation twelve hours before the examination and to use unusual care in the preliminary anaesthetization so that the small amount of sputum will not have been dislodged from the suspected bronchus prior to the bronchoscopy.)

Bronchography: Since a healing pulmonary tuberculosis occasionally produces bronchiectatic changes it may seem desirable to outline a portion of the bronchial tree by the instillation of iodized oil to establish an accurate diagnosis. It is suggested, however, that the least possible amount of oil be instilled to satisfactorily delineate the questionable area and that especial care be taken to avoid the overflow of excessive amounts of oil which might conceivably carry bacilli to other areas of the lung. As soon as the examination has been completed the patient should be placed on periodic postural drainage to remove the oil as quickly and completely as possible, lest its retention lead to an inflammatory reaction and possible subsequent production of pulmonary fibrosis. Although the literature reports occasional untoward effects from bronchography in pulmonary tuberculosis, it would appear that the desirability of making a correct diagnosis more than compensates for the minimal risk incurred, especially if careful technique is employed. The treatment of post-tuberculous bronchiectasis differs in no way from that of nontuberculous ectasia.

X-ray examination: It not infrequently happens that the original focus is hidden by overlying structures, thickened pleura or regenerated ribs and these should be investigated by complete diagnostic X-ray studies which may include postero-anterior and antero-posterior stereoscopic roentgenograms with overpenetration and/or Potter-Bucky diaphragm films; laterals; obliques; lordotics; spot films; varying tube angles and positions and tomography, always realizing that the original focus may have resolved beyond the point of absolute identification with any X-ray technique that is available at the present time. Occasionally also there is the patient who has a positive sputum but in whom no pulmonary lesion can be definitely identified. This situation will tax the diagnostic and therapeutic acumen to the utmost, but the patient should have the benefit of a detailed ear, nose and throat examination by a competent man.

What should be the management of the patient who has an occasionally positive sputum, even after careful and complete clinical reappraisal has revealed apparently adequate therapy and yet no obvious source of the bacilli? In the final analysis it would appear that economics largely determines the importance of this question. Do these patients actually get value received or do we as physicians honestly earn our fee at the current per capita cost per day? Should the patient who is fortunate enough to have a sick-benefit clause in his life insurance policy or who has hospital plan insurance be managed differently from the noninsured patient? Obviously we must be fair to the patient, to the insurance carrier and to ourselves. It is unfortunate that there are no published factual data on these questions and discussion must therefore necessarily be based on empiricism. It cannot be denied that many patients with only a few bacilli in the sputum can and do lead comfortable, useful and economically productive lives and do not infect other members of their households. It would seem grossly unfair both to the patients and to society to isolate indefinitely all such individu-

als in sanatoria and, conversely, it might be equally unfair to allow all of them to return to their former social environment. Who, then, shall be kept under treatment and who shall be discharged? In arriving at an equitable decision for any given individual due consideration must be given to the type, age and extent of the pulmonary lesion; the age, sex and resistance of the patient; his intellectual and economic status; his economic usefulness; his personal, family and civic responsibilities and finally to the type of work for which he has been trained.

It is predicated that the presence of any bacilli in the sputum of patients below the age of twenty-five is of very serious import and almost always indicates the necessity for further active treatment. It is also predicated that the tuberculosis sanatorium will employ as many of its former patients as may be possible.

The careless patient: We all know the sanatorium "repeater" who does well under close supervision but who throws discretion to the winds as soon as he is on his own. All too frequently he has a spread of his disease and an increase in the bacillary content of his sputum. Unfortunately there will always be a few among us who cannot or will not observe the rules of pulmonary hygiene or common decency and who can spread tuberculosis far and wide. These careless patients must be permanently isolated in spite of the fact that they have only an "occasional" positive sputum. The actual dollar cost of this may well be less than caring for the secondary contact cases. Then there is the patient who may have healed his disease by extensive fibrosis which reduces his pulmonary reserve to the point that he is a permanent respiratory cripple who can never be rehabilitated so he, too, must remain under custodial care.

Boarding home: A boarding home may be recommended for those patients who have no home and for those who have developed what amounts to a phobia of infecting their associates, especially if the boarding home is properly managed and preferably under the supervision of public health authorities.

Home: Finally there is the majority: they are intelligent; they are willing and anxious to assume their responsibilities; they have been thoroughly trained in pulmonary hygiene and they will conscientiously follow their instructions literally. These may be discharged to their homes to resume such physical activity as their physicians may direct, but this will be much safer if there are no children or young adults in the home and in no case should they be returned to employment that requires the handling of children or food, but instead they should be trained for some other type of economic usefulness.

Surgery: In very rare instances it may be necessary to give consideration to the possibility of surgical extirpation of a focus that may be shedding occasional tubercle bacilli, notably the post-tuberculous bronchiectasis but obviously these will be the most exceptional cases.

State subsidy: Dr. David Lyman once said that he would like to prescribe for the discharged patient with thousand dollar checks and what with the recent trend of social legislation this may not be entirely chimerical and it would almost certainly further safeguard the only recently healed lesion, but we would better not plan upon State Subsidy at least until the present national emergency is passed.

Follow-up: But the management of these patients cannot stop here. The physician has a moral obligation to see that treatment remains constantly adequate and, since so many patients suffer a relapse at the most unexpected moment, close and prolonged medical supervision is obligatory. Nor should the contacts of these patients be forgotten. Each should have periodic chest roentgenograms and all nonreactors to tuberculin should be retested annually in order to discover any possible development of disease early when adequate therapy may well prevent them from reaching the moderately and far advanced stages.

SUMMARY

If, after "apparently adequate" therapy, an occasionally positive sputum is found, attempts should be made to identify the source of the bacilli by bronchoscopy, using the retrograde lens; by bronchography and by a multiplicity of X-ray techniques.

Having failed to demonstrate the possible source of bacilli, there should be a complete reappraisal of the patient, giving due consideration to his economic and intellectual status to determine what equitable disposition should be made.

The careless and the incapacitated indigent who can never be rehabilitated must remain under custodial care; some may be discharged to boarding homes and others may be returned to their own homes to resume such physical activity as may be directed, but it will be necessary to see that therapy remains "adequate" and in no case should they be allowed to engage in occupations that require the handling of children or food. Prolonged supervision of their contacts is obligatory. And finally, surgical extirpation of a focus may be considered in the exceptional case.

SUMARIO

Si después de una terapéutica "aparentemente adecuada" obsérvase de cuando en cuando un esputo positivo, debe tratarse de identificar el punto de origen de los bacilos por medio de la broncoscopia, utilizando la lente retrógrada, la broncografía y varias técnicas roentgenológicas.

Si no se puede descubrir el posible origen de los bacilos, debe hacerse una nueva y completa justipreciación del enfermo, tomando en consideración su nivel económico e intelectual a fin de determinar cuál es la solución más equitativa.

El indigente descuidado e incapacitado que jamás se rehabilitará, debe continuar bajo custodia; a otros enfermos puede dárseles de alta a casas de huéspedes y otros pueden regresar a sus propios domicilios para continuar allí las tareas físicas que se les permitan, pero será necesario cerciorarse de que la terapéutica continúa siendo "adecuada," sin que jamás se permita dedicación a oficios que comprendan manejo de niños o de alimentos. También es obligatoria la vigilancia prolongada de los contactos. Por fin, en los casos excepcionales hay que tomar en cuenta la extirpación cruenta del foco.

MANAGEMENT OF PATIENTS WITH OCCASIONALLY POSITIVE SPUTUM AFTER APPARENTLY ADEQUATE THERAPY

Pathological Aspects[1]

HENRY STUART WILLIS[2]

It is obvious that the word sputum is open to various definitions. For the purpose of this discussion it should be assumed that we speak only of *bona fide* pulmonary secretions, collected intelligently by or from the instructed patient.

Sputum is pulmonary secretion. Shall we then not include the gastric contents and the stool, for sputum (and tubercle bacilli) are easily transferred to the gastrointestinal system, and bacilli found in these body excretions must in most cases have originated in the pulmonary lesion—the lesion for which adequate therapy is postulated in the terms of this panel.

In order that we may understand one another it is imperative that we define what we mean by positive sputum—or better, what method of examination yielded the positive or negative report. Was direct smear negative on a specimen brought by the untutored patient, or was the test such that reasonable assurance could be given of a lesion that no longer sheds tubercle bacilli? Should we be satisfied with the report which says merely: "Sputum positive" or "Sputum negative?" Should not the answer be negative (or positive) by whatever method was used—direct smear, concentration, culture or guinea pig inoculation —and should it not be stated whether determination was made on a single or pooled specimen and/or a statement made of the number of such specimens studied? Such detailed statement carries a great deal of clinical value and prognostic importance.

With such definition as a basis, one might ask what are the sources of occasionally positive sputum. Since this is to be a discussion of the pathological features of the panel question, let us consider with the greatest possible brevity what collapse does to tuberculosis, for in these days adequate therapy includes the extensive employment of collapse measures. How does collapse affect tuberculosis? In the first place it exerts the mechanical effect of closing cavities and thus prevents easy egress of bacilli through bronchi: it holds the cavity walls in contact and in this way facilitates fibrous symphysis of the walls. Sometimes cavities are said to "heal" under collapse by contracting upon their content of material which undergoes inspissation. This material may soften and become evacuated. During such times the sputum usually contains bacilli.

Collapse and body rest prevent overexpansion or stretch and lessen motion; they thus lessen the pull and reduce the tension on young scar, favor its more perfect formation and encourage healing. As healing occurs, areas of tissue damage or destruction become surrounded or infiltrated by fibrous tissue. On

[1] Presented in the Panel Discussion before the Medical Section at the 38th annual meeting of the National Tuberculosis Association, Philadelphia, Pennsylvania, May 6, 1942.

[2] Wm. H. Maybury Sanatorium, Northville, Michigan.

the average the patient with positive sputum who recovers (with or without collapse) loses his bacilli gradually as the process of healing takes place. In the successful case the time comes when no bacilli are cast off from the lesion. In a distressingly large number of cases, however, bacilli are present occasionally.

The process of healing or nonhealing is irregular, not continuous. In one part of a lesion fibrous tissue may be deposited while in another part, tissue destruction may occur. Fresh, exudative lesions may absorb rapidly in one area and slowly in another. Even after treatment can be called adequate, a small area of tissue destruction or caseation may shed a few bacilli and begin promptly to undergo healing. This process could recur several times in a given person.

A lesion may be held in relative control by pneumothorax, the sputum may meantime be negative and the lesion grow smaller in the film. Too much reëxpansion between refills could lead to stretch of the lesion or tear of young scar and release bacilli for a short time.

Crushing of the phrenic nerve may facilitate fibrosis by adding to pulmonary rest, lessening pulmonary ebb and flow of normal respiration. Healing proceeds satisfactorily; the lesion grows smaller, the exudative character changes by absorption, scar is laid down and treatment is called adequate. It may or may not be adequate at the moment of evaluation, depending upon the pathological status of the lesion and the strength or toughness of the scar. Often the situation remains well in hand and the patient is returned to society sound in body. Occasionally, conditions being right, returning motion of the diaphragm produces tug upon the young fibrous tissue that binds the lesion or holds the cavity walls together. This tug or strain is sufficient to break the new formed tissue and release bacilli for a long or a short time. In this circumstance, treatment is no longer adequate and this might lift the case out of the group under discussion.

A number of conditions associated with tuberculosis of the lungs may produce occasional positive sputum when treatment is adequate, although it is the rule that these conditions, when they shed bacilli, do so constantly rather than intermittently or occasionally. Time will allow little more than their mention: they are tuberculosis of the bronchus, which is present usually as ulcer, tuberculoma or granulation tissue; tuberculosis of the trachea, of the larynx, and finally bronchiectasis. One encounters (fortunately not very often) the case in which bronchiectasis develops at and around the seat of former tuberculosis. Such a patient, prone to pneumonitis in the area, may raise tubercle bacilli on these occasions (as also may any tuberculous patient with a heavy chest cold). Then, if all goes well upon the subsidence of the inflammation, sputum promptly becomes negative again and remains so.

Of necessity this discussion is fragmentary and brief.

MANAGEMENT OF PATIENTS WITH OCCASIONALLY POSITIVE SPUTUM AFTER APPARENTLY ADEQUATE THERAPY

Nursing Aspects[1]

ESTA H. McNETT[2]

The management of patients with occasionally positive sputum after apparently adequate therapy is primarily a medical problem. The nurse's greatest contribution is to be made probably by being of assistance to the physician.

Tuberculosis is unique among communicable diseases in the fact that its transmission from one person to another depends in large measure upon the dosage of bacilli and repeated opportunities for infection rather than upon a single exposure. Intelligent patients with occasionally positive sputum need not be a serious menace to members of their families or other associates if they have been properly educated.

The nurse's responsibility in the institutional care of patients with occasionally positive sputum after apparently adequate therapy is the same as is the care of other tuberculosis patients as long as they remain in the hospital. Their general physical condition must be considered and nursing care given in quantity and quality adequate to meet their individual needs. This may include complete bed-side nursing care at times or the application of an occasional treatment.

The proper collection of specimens is an important procedure and should be given careful consideration by the nurse. Some patients produce a small amount of thick sputum only once in several days. The observation of physical signs and the accurate recording of subjective and objective symptoms are valuable aids to the physician which may be given by the nurse because of her intimate and prolonged contact with patients during their daily routine care.

Patients with only an occasionally positive sputum may need an unusual amount of encouragement and bolstering of morale because of the uncertainty in regard to the status of their disease and the need for submitting to troublesome diagnostic procedures such as bronchoscopy and bronchography. Temporary or permanent collapse therapy measures may be required and complications may arise.

Parallel in importance from the nurse's point of view to meeting the physical needs of patients with an occasionally positive sputum is that of helping them to learn to live safely with others. The education of most patients may be handled best on a personal basis. Few physicians have time to give individual instruction to many patients. A well qualified nurse may accomplish much in a hospital by meeting such patients singly upon admission and giving instruction in regard to the technique of controlling the dissemination of infectious organ-

[1] Presented in the Panel Discussion before the Medical Section at the 38th annual meeting of the National Tuberculosis Association, Philadelphia, Pennsylvania, May 6, 1942.

[2] Lowman Memorial Pavilion, City Hospital, Cleveland, Ohio.

isms, the importance of rest and a general orientation to the routine of institutional life. For some individuals a simple conversation, "the telling method," indicating the technique necessary for the hygienic control of cough and care of expectoration is all that is required. Many patients, however, need repeated instruction and encouragement including demonstrations in regard to handling of tissues to cover their mouths when coughing and specific instructions in regard to the proper methods of disposing of their expectoration. Such patients should be so thoroughly trained in the proper hygienic methods that hygienic procedures become a part of their normal behavior patterns. This type of training may be accomplished best in a tuberculosis hospital where good fundamental principles of hygiene are followed.

The simple motto of "clean supplies, with clean hands, to every patient" has been found to be useful in educating members of the lay personnel in some institutions in regard to clean techniques and has likewise influenced the thinking of patients. There is the occasional patient who cannot be made to feel any responsibility in regard to the protection of others and cannot be trained to use good methods of hygiene in disposing of his oral discharges. Isolation is the only alternative for such individuals.

Tuberculosis presents a real problem in nursing education. Institutions housing the number and variety of tuberculosis patients adequate to present a good clinical field in which to educate student nurses always have so many open cases of tuberculosis that a rigid program of aseptic technique is the only safe course to follow. However, since dosage is the controlling factor in the transmission of tuberculosis, judgment must be used in the handling of individual patients, such as those with occasionally positive sputum. The burden of this particular task is apt to fall upon the public health nurse as she follows discharged patients into their homes.

Before we can expect many nurses to be prepared to exercise the judgment which is required in the education of tuberculosis patients to live safely with others, it will be necessary to extend the preparation of nurses in this particular field. Organized instruction and clinical experience in tuberculosis is planned for only a small proportion of the students in schools of nursing in the United States at the present time. More than a third of the nurses who graduate each year have no experience in either tuberculosis or acute communicable disease, and are, therefore, not equipped to make practical applications in regard to the problems created by tuberculosis control.

MANAGEMENT OF PATIENTS WITH OCCASIONALLY POSITIVE SPUTUM AFTER APPARENTLY ADEQUATE THERAPY

Public Health Aspects[1]

KENNETH M. SODERSTROM[2]

That there has been, or will be, overlapping of the substance of these papers this afternoon is not at all disconcerting. This overlapping is unavoidable and at the same time valuable. It serves to emphasize and reëmphasize certain points of importance. As it affects this paper it proves that there is no distinct demarkation between the public health aspects and the clinical or pathological points of view. They must overlap in practice if our tuberculosis work is to succeed beyond its present successes.

From a public health point of view those cases that we are discussing are, in reality, more than just occasionally positive sputum cases. They are cases in which our laboratory technicians, or ourselves, only occasionally find the tubercle bacilli in their sputa samples. We would be well advised to consider them simply as positive sputa cases, but cases in which the danger of contagion can be made insignificant as compared with some other classifications of active cases. These are, of course, active cases of tuberculosis.

What do we mean by occasionally positive sputum cases? For those clinicians who follow their cases with the use of the direct smear technique with sputum samples at certain intervals, this has one meaning. To those discontent with any procedure less satisfactory than the most carefully regulated concentration technique with culture, this has another meaning. One sanatorium may report a conversion rate much more impressive for its treated active cases than another. However, unless this sanatorium uses the same technique for finding occasionally positive sputa, as others, there are no grounds for comparison.

The writer has been informed by others and has learned from personal investigation that to-day, whenever carefully executed concentration and culture technique are employed, positive sputum findings occur in cases which would have previously met all of the requirements for classification as "arrested," or even in some instances as "cured." This finding becomes more illuminating when routine concentration and culture is made of stomach contents before conversion is said to be a fact. It has been reported that gastric lavage has revealed upward to 25 per cent of those cases said to be negative by concentration and culture of expectorated sputa to be in reality positive cases (1).

From the standpoint of preventive medicine this problem of when is a case truly negative for tubercle bacilli and when is he occasionally positive, is obviously very important. We cannot be too careful in our methods for determining

[1] Presented in the Panel Discussion before the Medical Section at the 38th annual meeting of the National Tuberculosis Association, Philadelphia, Pennsylvania, May 6, 1942.

[2] Medical-Dental Building, Seattle, Washington.

this point. To inform a patient that his sputum is free of tubercle bacilli is to assume a large amount of public health responsibility. One must leave no stone uncovered in searching for the infectious agent responsible for the perpetuation of tuberculosis.

It is recognized by the writer that in all probability, as long as we have clinical tuberculosis, we are going to have cases that fit all of the classifications of an arrested case, except for the discouraging occasionally positive sputum finding. Such cases are often the end result of our most adequate forms of treatment and reflect no criticism on the care rendered the patient. But what to do with these cases is a vexing problem for the health officer as much as for the internist and surgeon. We cannot keep them housed in sanatoria indefinitely. In each case we are faced with reality in its most scanty attire.

The word "education" as used by tuberculosis workers seems to many of us ambiguous. The bulk of health education seems to be directed at refractory objects, that is, groups of healthy people. We should and do find, in our clinical cases and their families, people ready and willing to absorb practical personal health education. These people have a reason to be interested in such education. It should be given to them in generous quantities and yet all too frequently it is taught in our sanatoria only by means of reluctant answers to the patients' questions. When a sanatorium prides itself on its methods of patient education, investigation will usually show that this consists of a group education plan; which plan allows each patient to apply generalities to fit his own case. Being untrained in the basic principles of pathological physiology, misconstrued application of this medical information is the rule. With our patients who present the problem of an occasionally positive sputum this is no exception. Here we have a patient that we feel from a public health point of view cannot be trusted. We feel that if we trust him to travel at large in society he will infect others; yet we admit a deficiency in our ability to cure him to the point of noninfectiousness. We therefore have no right, as medical experts, to condemn him to isolation from his fellow men. With the exception of that rare antisocial rascal who would willingly see his fellow men all ill as he is, isolation is not necessary. Personal education can be made the answer to the problem. This is not accomplished by the distribution of pamphlets, nor by the occasional talks over the sanatorium radio hook-up. This type of case needs to understand his personal problem just as much as the diabetic needs to understand his. He needs to be schooled in it. Just as the diabetic must understand the pathological physiology of his own body so that he may survive, so does the tuberculous victim with the occasionally positive sputum need to understand his that he may go free without danger to his fellow men.

The opportunity for schooling the type of patient under discussion is in the sanatorium. There is no excuse for not doing so. The patient's physician has months and weeks to visit at the bed-side or in his own office with this type of patient, discussing with that patient his personal problems. If, when time for discharge arrives, the patient, assuming he is mentally sound, is not educated in

and sold on the technique of preventing the spread of his disease to others, the physician in charge should consider himself as failing to meet his obligation in the management of this case.

The rational belief that proper education answers the public health aspect of this problem is found in certain epidemiological studies. The idea that the tubercle bacillus is as infectious as the viruses and organisms of our common contagious diseases has never appealed to many of us. Certainly there is adequate proof to-day that nobody need hold to this concept. The work of Brailey in Baltimore, to cite one study, is quite convincing in its findings (2). She was able to show, after years of follow-up study on children in tuberculous households, that there is a direct relationship between the amount of infection produced among contacts and the stage and duration of disease in the individual. Even those patients diagnosed for the first time with advanced disease and constant positive sputum failed, after months of contact, to produce universal infection among their own household contacts. Likewise, when the disease was early and comparatively few tubercle bacilli reported in the sputum, the rate of contact infection was relatively low. These studies were made among peoples of the lowest income bracket and in whom little or no tuberculosis education had been instilled. The excellent work that has been done in Tennessee has revealed this fact, the reports of which are available in our national literature (3).

A study, reported by Cox and Thorton from the writer's home state based upon tuberculin studies among college students, reveals by indirect analysis findings quite comparable to those of Brailey (4). It was shown that the percentage of tuberculin reactors paralleled the history and amount of exposure known to have occurred in the home. Even when certain individual students had lived in tuberculosis households until the patient had died there was far from a universal infection rate. One could cite numerous other epidemiological studies to prove this point but it seems hardly necessary.

If universal infection among contacts of undiagnosed advanced cases is not the rule, it would seem that universal lack of infection among contacts of the well educated patient with only an occasionally positive sputum could be made the rule. All of us doing clinical work have followed certain continuously positive sputum cases for years in which the patient's progeny have remained tuberculin-negative. Several doctors are known to the writer who have had clinical disease with positive sputum over a period of from a few to several years and yet their children remain negative to tuberculin. It should seem to all of us then, that given a case with only occasionally positive sputum, that such can be rehabilitated and permitted to go among society free of a leper's stigma.

Of course, there will always be those who say that these words cannot be made to apply to all cases because so many of our patients come from an intellectual as well as economic stratum far below the national average. This intellectual point is debatable (5) but, assuming it is so, one may see the results of training in another chronic disease and get from that, much encouragement. Diabetes and what has been done with that problem, shows the value of personalized educa-

tion. Many of our authorities on diabetes report more gratifying results with children, uneducated foreigners and even adults with children's minds, than with those of so-called higher intellectual faculties. Perhaps the former do not have ideas of their own. We must remember, when we are determining the mental level of our tuberculous patients and are determining from this consideration what to expect from them, that among the intelligentia known as college professors, a surprisingly high percentage are Christian Scientists. Scholastic background has little or no value in the schooling of the tuberculous in regard to his obligations to his fellow men. Admiration, respect and faith in the teacher produces social consciousness. Without this, the patient with only an occasionally positive sputum may hardly appreciate the need for the hygienic control of cough and expectoration.

At time of discharge from the sanatorium this type of patient must be carefully followed for two reasons: first, for his own personal good and, second, that of his contacts. It would be highly advantageous for such a patient to become acquainted with the public health nurse assigned to his future residential locality prior to his sanatorium discharge. A conference at this time with the nurse, the patient and the physician could assure coöperation in the future and destroy in advance any chance of the patient's feeling the calls at his home are of a snooping nature. Home visits of such a nature are imperative if we are to observe the fruits of our teaching. The writer's observation of administrative programs of numerous sanatoria reveals an unnecessary hiatus between the home and the sanatorium, even when both are in the same metropolitan area. Obviously patients returning from distant sanatoria have a disadvantage in this respect. It is felt that the public health nurse is not used enough in the follow-up of our discharged patients and their contacts. This is particularly true of those returning to some gainful occupation, yet these must not be forgotten.

The question of rehabilitation might enter into this discussion though one justifiably wonders if it truly is a public health problem. Rather, it may be considered a social welfare worker's responsibility. However, it should be that the physician's interest in his sanatorium patient extends into the patient's future life and therefore rehabilitation problems are not so remote from an adequate clinical program. The desire to prevent tuberculosis in others should motivate the physician to lend all possible support to plans aimed at rehabilitation of these patients now under discussion. The educational plea emphasized so strongly in this paper is imperative if any rehabilitation program is to succeed from the patient's standpoint, at least. For example, the nursemaid and school teacher must understand why their rehabilitation must be directed away from their professions just as our "typhoid Marys" must understand why they should no longer be food handlers.

The sanatorium most certainly is the place to set the scene for the long program of rehabilitation. This is not to be restricted to the efforts of the local occupational therapy director.

SUMMARY AND CONCLUSIONS

A definition of the case with occasionally positive sputum is necessary. This must include an evaluation of the technique of sputum examination. A group of such patients examined by one laboratory may mean sputum-negative cases, but to another the same group would be classed as occasionally positive-sputum patients. One must then come to the conclusion that, until our laboratory techniques are all improved and all identically employed, we had better consider most of our arrested cases, as well as other types, as probable sputum-positive cases and educate them accordingly. Further, we haye no reason to conclude other than such patients, properly taught and educated in the hygienic principles of cough and sputum control, can live with and contribute to the betterment of our society without infecting others. Education of the patient in question in his responsibility for the protection of others is described as the real solution to the problem of such cases from a public health standpoint. We are faced with the fact that if such patients are discharged from our sanatoria without the proper education we, as clinicians, have not contributed our best in our community. We should also admit that the discharge of a recalcitrant, unsocial patient cannot be construed as a compliment to our professional ability. A plea is made to utilize the public health nurse to bridge the gap between the sanatorium, the home and these patients' places of occupation. Only part of the responsibility of social rehabilitation of such cases rests with the medical profession.

SUMARIO Y CONCLUSIONES

Se necesita definir bien el caso cuyo esputo es ocasionalmente positivo. Esto debe comprender una avaluación de la técnica del examen del esputo. En un laboratorio esos enfermos pueden ser clasificados como de esputo negativo, mientras que en otros el mismo grupo sería clasificado como ocasionalmente positivo. Tenemos, pues, que convenir en que hasta que nuestras técnicas de laboratorio sean perfeccionadas y se empleen idénticamente, es mejor considerar a la mayor parte de los casos estacionados así como a otros tipos como probablemente de esputo positivo y educarlos desde ese punto de vista. Además, no tenemos motivos para aceptar otra conclusión sino la de que estos enfermos, debidamente educados en los principios higiénicos del dominio de la tos y del esputo, pueden vivir en el seno de la sociedad y contribuir al adelanto de ésta sin infectar a sus semejantes. La educación de esos enfermos a fin de que comprendan la obligación que tienen de proteger al prójimo, constituye la verdadera solución del problema desde el punto de vista sanitario. Nos confronta el hecho de que, si se da de alta a esos enfermos de nuestros sanatorios sin la educación que necesitan, como clínicos no hemos hecho lo que debiéramos en pro de la colectividad. Debemos también reconocer que el alta de un enfermo recalcitrante y asocial no debe ser interpretada como demostración de nuestra capacidad profesional. Abógase por la utilización de la enfermera sanitaria para que colme la laguna entre el sanatorio, el hogar y el sitio de trabajo de esos enfermos. A

la profesión médica sólo le corresponde parte de la responsabilidad que entraña la rehabilitación social de esos enfermos.

BIBLIOGRAPHY

(1) Dunn, W. T.: Personal communication.
(2) Brailey, Miriam: A study of tuberculous infection and mortality in the children of tuberculous households, Am. J. Hyg. 1940, *31*, 1.
(3) Stewart, H. C., *et al.*: Tuberculosis studies in Tennessee. Infection and mortality in the families of the tuberculous, Ibid., 1937, *26*, 527.
(4) Cox, S. L., and Thornton, J. E.: Tuberculin testing results for 3,421 college students, State of Washington, 1935 to 1938, Journal-Lancet, 1940, *60*, 165.
(5) Mustard, H. S.: Report on Study of Tuberculosis Problem and Control Program, Cattaraugus County, New York, May 16, 1940, Cattaraugus County Health Department.

MEDICAL ASPECTS OF THE REHABILITATION OF THE TUBERCULOUS[1]

The Experience of a Quarter Century with 964 Patients at Altro Work Shops

LOUIS E. SILTZBACH[2]

In 1912 the Board of Trustees of the Montefiore Country Sanatorium at Bedford Hills, New York, undertook a follow-up survey of patients with pulmonary tuberculosis who had been discharged as arrested or quiescent. A shock awaited the trustees. One-half of the patients had either died or suffered a recurrence of disease within twelve to eighteen months following discharge. These findings led to the establishment of the Committee for the Care of the Jewish Tuberculous of New York.

On June 14, 1915, Altro Work Shops, a model garment factory, opened its doors to 22 former sanatorium patients. The principles underlying the founding of Altro Work Shops have guided the Committee in its work to the present day. (For a detailed description of the operation of the Altro Work Shops see (5, 6).)

Industrial convalescence as a method of after-care for patients recovering from chronic illness or disabling injury rests upon sound physiological and psychological bases. This form of rehabilitation is particularly applicable to the tuberculous; for they have a physical handicap engendered by the inactivity which is so great a part of the treatment of the disease and they are mentally insecure because of the hazard of a recurrence of illness.

The workshop seeks to overcome the physical handicap by prescribing graduated work. Against the anxiety it uses principally two measures. One is the closest medical supervision of the patient approximating that of the sanatorium. The other is complete family supervision, including a subsidy supplementing the patient's earnings until he becomes self-supporting. In general, the workshop offers the post-sanatorium patient temporary sheltered factory employment through which he may condition himself, physically and psychologically, in preparation for his return to every-day life. Whenever necessary, the course at the workshop is followed by a period of vocational training.

The purpose of this paper is to show how such a group of patients with pulmonary tuberculosis fared during their stay at the workshop where they were productively engaged, and later when they left to take jobs on the outside. The analysis is based on the experience of all tuberculous patients who worked at Altro beyond a three months' probationary period during the years 1915 to 1939. Nine hundred and sixty-four patients were admitted for the first time during

[1] Presented before the Joint Session of the Medical and Administrative Sections at the 38th annual meeting of the National Tuberculosis Association, Philadelphia, Pennsylvania, May 9, 1942.

[2] Committee for the Care of the Jewish Tuberculous, 71 West 47th Street, New York, New York.

this period and, where possible, they were followed to the closing date of the study, July, 1941.

The longest period of observation was twenty-five years after discharge from the workshop. The average period of observation was 7.8 years. Ninety-seven per cent of the patients were traced to the end of five years and 92 per cent could be traced ten years.

Because of the extended period of observation it was decided to divide the patients chronologically into two groups: those admitted to the workshop in the years 1915 to 1929—a group of 445 patients; and those of the years 1930 to 1939—519 patients. Such a division differentiates the patients of the precollapse therapy era from those of the period wherein collapse therapy is prominent.

DESCRIPTIVE DATA

Before discussing the experience of patients during their stay at Altro and that of the post-Altro years we will describe them as they were up to the point of admission to the workshop.

Sex: There were 705 male patients and 259 female patients.

Marital condition: Three of every five males were married at admission, but only one of six of the female patients.

Age: Half of the patients were under thirty years of age at Altro admission. The median age for the male patients was thirty-three years; for the female patients twenty-five years; 97 per cent were between the ages of fifteen to forty-nine years.

Occupation: Of the Altro patients who were employed before their illness, 41 per cent were either garment workers or workers in some related sewing trade. Other large occupational groups were clerks, salesmen, semiskilled operatives and laborers.

Length of stay at sanatorium: Altro patients are accepted from all sanatoria but, because of the close working arrangements with the Montefiore Country Sanatorium, 62 per cent of our patients came directly from this institution. The median stay at all sanatoria preceding Altro admission was 14.4 months. In the earlier period, the median stay was 11.3 months; and in the later period 16.8 months. About 6 per cent of our patients had no sanatorium experience or remained in an institution for less than thirty days. Many of the patients without previous sanatorium experience before Altro had been treated in rest cottages. All the patients had some treatment previously.

Treatment before Altro admission: The type of treatment received by the patients before Altro admission differs markedly in the two periods. Only about 6 per cent of the patients received collapse therapy (pneumothorax only) among the group admitted to the workshop from 1915 to 1929. (Patients with six months or longer of pneumothorax therapy are included.) In the later group, 1930 to 1939, 52 per cent of the patients had received some form of collapse therapy; 40 per cent had pneumothorax, 7 per cent had thoracoplasty and 5 per cent had phrenic nerve operations; 160 patients came to Altro with pneumothorax. Three-quarters of these patients continued to receive their refills throughout their Altro stay.

From the date of sanatorium discharge to the date of admission to the workshop, there was a median time interval of 4.3 months. The median stay at the workshop was 16.8 months.

Before presenting the facts on the clinical classification of our patients, we should like to point out that the pre-Altro sanatorium data were reëxamined and classified to conform to the present-day Diagnostic Standards of the National Tuberculosis Association.

Stage of disease: At Altro admission, 21 per cent of the patients had disease which was minimal in extent, 42 per cent moderately advanced and 37 per cent were far advanced. Thus 4 out of 5 of our patients came to us in the moderately or far advanced stage of disease.

Condition or clinical status on admission: With regard to the patient's clinical status or condition on admission to the workshop, 64 per cent were arrested, including a few apparently cured, 11 per cent apparently arrested, 17 per cent quiescent, and 8 per cent unstable or frankly active. Differences between patients of the periods 1915 to 1929 and 1930 to 1939 will be discussed later.

Sputum history: The clinician at the bed-side directs his therapy primarily at closing the patient's cavity and ridding him of his positive sputum. Sputum conversion has become the touchstone of successful treatment in pulmonary tuberculosis. Therefore, in addition to the two classifications cited, that is, stage and condition, it was found useful to employ a third grouping relating to the patient's sputum history before admission to the workshop.

The patients were divided into three groups: first, patients who never had a positive sputum and still had a negative sputum when admitted to the workshop—"minus-minus" group; second, patients who had not been rid of their positive sputum at admission to the workshop—"plus-plus" group; third, those remaining patients who had a positive sputum some time during their illness which had been successfully converted to a negative sputum before admission to the workshop—"plus-minus" group. Such grouping contains an unknown degree of error, since the frequency of sputum examinations and refinements in the bacteriological technique employed varied from sanatorium to sanatorium and changed from period to period.

At admission to the workshop, 30 per cent of the patients were in the minus-minus group, 15 per cent were in the plus-plus group and 55 per cent in the plus-minus group (table 1).

There were significant differences in this regard between the two periods of 1915 to 1929 and 1930 to 1939. In the early period one-fourth of the patients admitted to the workshop were in the plus-plus group, while in the later period this was reduced to 6 per cent. Even more striking was the contrast between the two periods for patients who had previously had a positive sputum with successful conversion before admission to the workshop. In the earlier period, 38 per cent of our patients were in this group. In the later period, this rose to 69 per cent. This went hand in hand with a rise of the percentage of arrested cases from 55 per cent in the 1915–1929 period to 70 per cent in the 1930–1939 period and a drop in the percentage of unstable patients from 14 per cent in the earlier period to 3.5 per cent in the later period.

The improvement in clinical status and sputum conversion rates of our patients on admission to the workshop has a historic background. In the early period, before the frequent use of serial chest X-ray films and refined bacteriological methods, sanatoria were discharging a relatively higher proportion of patients with positive sputum and unstable lesions and consequently Altro was accepting a proportion of them for work therapy. In the later period, the increase in admission to the workshop of patients with arrested disease and with successfully converted sputum simply reflected the sharpening of criteria for sanatorium discharge and for Altro admission. This improvement in the status of patients in the collapse era is a world-wide phenomenon. It is present in the British, Dutch, Swiss and German sanatorium statistics. The workshop, then, is devoting itself increasingly to the plus-minus, arrested groups of patients, who can be expected to reap the greatest profit from a temporary rehabilitation course.

The foregoing analysis of the status of our patients on admission to the workshop indicates that the group as a whole was not unduly weighted by patients in the more favorable categories. They may be considered a representative cross-section of the type of patient rehabilitation offices are called upon to help.

TABLE 1

Sputum history at Altro admission

CLASSIFICATION OF SPUTUM HISTORY AT ALTRO ADMISSION	PER CENT			NUMBER		
	Both periods 1915–1939	Admitted 1915–1929	Admitted 1930–1939	Both periods 1915–1939	Admitted 1915–1929	Admitted 1930–1939
Total patients	100.0	100.0	100.0	964	445	519
Minus-minus	30.5	37.3	24.8	287	160	127
Plus-plus	14.8	24.9	6.3	139	107	32
Plus-minus	54.7	37.8	68.9	515	162	353
Sputum history unknown				23	16	7

SURVIVAL RATES

To study the general mortality, and the tuberculous morbidity and recurrence rates of our patients, I used an adaptation of the modified life-table method as suggested by Frost (1), and applied by Downes (2), Hilleboe (3) and others. A series of charts is presented to show the survival rates, based on this method, of patients classified according to stage of disease, sputum history and clinical condition at Altro admission. Chart I shows the rate of survival annually up to ten years post-Altro, related to stage of disease (tables 2, 3, 4).

At the end of ten years, 87 per cent of the patients with minimal tuberculosis had survived and 86 per cent of the moderately advanced patients. The survival rates for patients in these two stages of disease were almost identical throughout the period.

The rate of survival for patients with far advanced disease was markedly different. It decreased steadily and fairly rapidly; at the end of ten years, 63 per cent of these patients were alive.

Chart II shows the rate of survival related to the sputum history of patients at Altro admission.

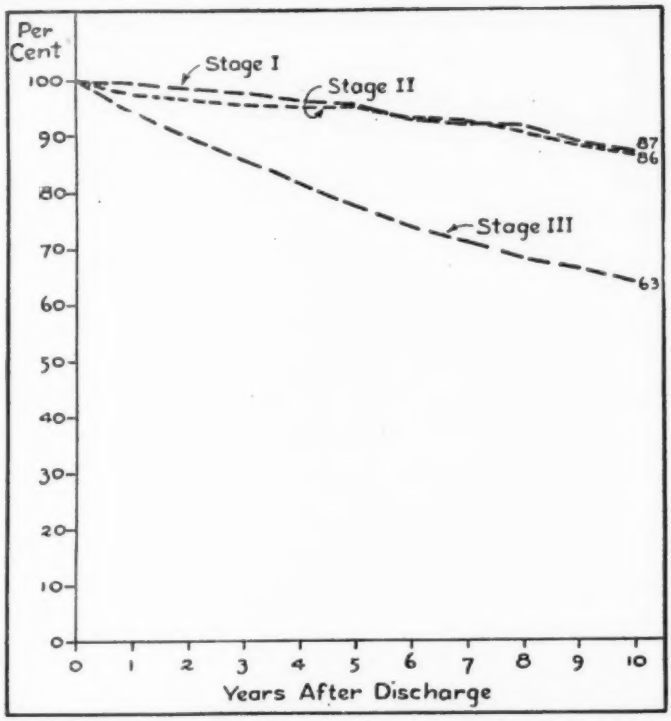


CHART I. Survival rates of patients post Altro according to stage at admission

TABLE 2

Survival rates after discharge from Altro of patients having minimal tuberculosis on admission to Altro

YEARS AFTER DISCHARGE	PERSONS AT BEGINNING OF YEAR	NUMBER WITHDRAWN DURING YEAR	AVERAGE NUMBER OF PERSONS AT RISK DURING YEAR	NUMBER OF DEATHS	PERCENTAGE DYING DURING SELECTED YEAR	PERCENTAGE SURVIVING THROUGH PAST AND SELECTED YEARS
1	201	10	196.0	1	.51	99.49
2	190	14	183.0	2	1.09	98.41
3	174	2	173.0	1	.58	97.84
4	171	4	169.0	3	1.78	96.10
5	164	5	161.5	1	.62	95.50
6	158	7	154.5	5	3.24	92.41
7	146	6	143.0	1	.70	91.76
8	139	11	133.5	1	.75	91.07
9	127	5	124.5	4	3.21	88.15
10	118	10	113.0	2	1.77	86.59

At the end of ten years, 84 per cent of both minus-minus and plus-minus groups of patients were alive. There is close approximation of the survival rates for patients in these two sputum groups throughout the period.

The survival rate of patients admitted to the workshop with a positive sputum, plus-plus group, is different throughout. The rates decreased sharply in the early years post-Altro and at the end of ten years 54 per cent of these patients had survived.

TABLE 3

Survival rates after discharge from Altro of patients having moderately advanced tuberculosis on admission to Altro

YEARS AFTER DISCHARGE	PERSONS AT BEGINNING OF YEAR	NUMBER WITHDRAWN DURING YEAR	AVERAGE NUMBER OF PERSONS AT RISK DURING YEAR	NUMBER OF DEATHS	PERCENTAGE DYING DURING SELECTED YEAR	PERCENTAGE SURVIVING THROUGH PAST AND SELECTED YEARS
1	397	17	388.5	9	2.32	97.68
2	371	27	357.5	4	1.12	96.59
3	340	29	325.5	4	1.23	95.40
4	307	23	295.5	1	.34	95.08
5	283	29	268.5	0	0	95.08
6	254	32	238.0	6	2.52	92.68
7	216	31	200.5	1	.50	92.22
8	184	27	170.5	4	2.35	90.05
9	153	28	139.0	4	2.88	87.46
10	121	27	107.5	2	1.86	85.83

TABLE 4

Survival rates after discharge from Altro of patients having advanced tuberculosis on admission to Altro

YEARS AFTER DISCHARGE	PERSONS AT BEGINNING OF YEAR	NUMBER WITHDRAWN DURING YEAR	AVERAGE NUMBER OF PERSONS AT RISK DURING YEAR	NUMBER OF DEATHS	PERCENTAGE DYING DURING SELECTED YEAR	PERCENTAGE SURVIVING THROUGH PAST AND SELECTED YEARS
1	350	20	340.0	19	5.59	94.41
2	311	22	300.0	14	4.67	90.00
3	275	20	265.0	12	4.53	85.92
4	243	19	233.5	12	5.14	81.50
5	212	18	203.0	10	4.93	77.48
6	184	22	173.0	9	5.20	73.45
7	153	21	142.5	5	3.51	70.87
8	127	17	118.5	5	4.22	67.88
9	105	13	98.5	3	3.05	65.81
10	89	9	84.5	3	3.55	63.47

These curves indicate that patients who have had a positive sputum some time during their illness which had successfully been converted to a negative sputum before admission to the workshop (plus-minus group) have survival rates quite as favorable as those of patients who have never had a positive sputum (minus-minus group). A similar experience is reported by British observers (4).

In this country, Hilleboe (3) has studied 4,550 patients discharged alive from

Minnesota sanatoria in the years 1926–1935, and reported the survival rates according to sputum on sanatorium discharge for patients in each stage. The Minnesota data clearly demonstrate the greater prognostic importance of the patient's sputum history as compared with his stage of disease. Thus, 81 per cent of the far advanced patients with negative sputum on sanatorium discharge were alive at the end of five years, but only 44 per cent of the patients in the moderately advanced stage who were discharged with a positive sputum.

Chart III shows the rates of survival annually up to ten years post-Altro related to condition of patients at Altro admission. Of the patients classed as

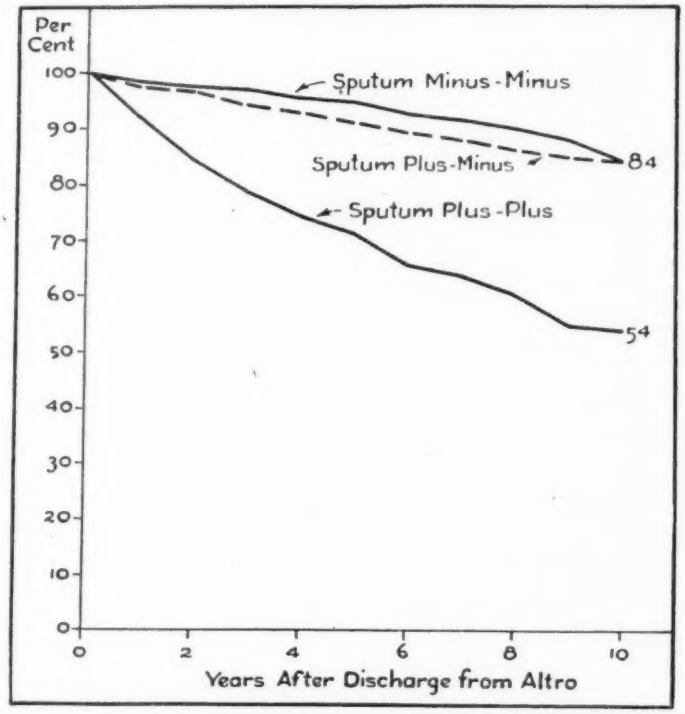


CHART II. Survival rates of patients post Altro according to sputum on admission

arrested and apparently cured, 86 per cent were alive at the end of ten years. For patients who were quiescent or apparently arrested, the proportion was slightly smaller, 78 per cent, but only 34 per cent of the unstable, frankly active patients were alive at the end of ten years.

As previously stated, the unstable patients belong to the early period of the workshop's operation. The poor prognosis of patients with open cavities and unstable lesions, as shown by serial X-ray examination, is common knowledge to-day. Such patients either require further treatment at an institution or custodial isolation.

MORTALITY OF ALTRO PATIENTS COMPARED WITH THAT OF THE GENERAL POPULATION

The mortality of our group after discharge was compared with that of the general population. The results are expressed in ratios of the actual deaths to the number expected in a population of the same size and same composition of sex and age. Our standard of comparison was the white population of New York City during the period covered by this study. (The average mortality of the years 1922, 1923 and 1924, and 1933, 1934 and 1935 were used.) For the entire experience the mortality of the Altro patients was about twice that of the

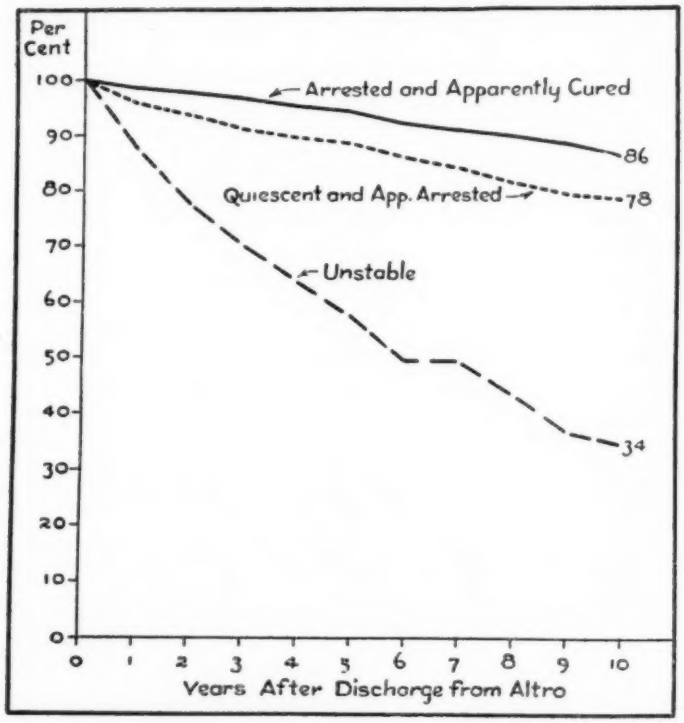


CHART III. Survival rates of patients post Altro according to condition at admission

general population (table 5). No essential difference was found between the two sexes, all ages combined, when allowance was made for the lower average age of the women in this experience.

Among Altro patients in the aggregate the ratios were highest in the third decade of life, deaths being six times the expected rate at that age period. The ratios declined steadily and at forty-five years and over our patients experienced about the same mortality as persons of the same age in the general population.

When stage of disease was considered, Altro patients with minimal disease were found, in the aggregate, to have a mortality experience not unlike non-tuberculous persons in the general population, the ratio being only 1.04 (table 6).

The patients in the moderately advanced stage had, in the aggregate, a mortality rate of one and one-half times that expected in the general population (ratio 1.53) and for the patients in the far advanced stage, it was four times that of the general population (ratio 4.01).

TABLE 5

Ratio of actual to expected deaths from all causes among patients discharged from Altro, 1915–1939[1,2]

AGE GROUPS	ALTRO ADMISSIONS 1915–1939			RATIO OF ACTUAL TO EXPECTED DEATHS
	Years of life exposed	Actual deaths	Expected deaths	
All ages	9,269.5	180	85.71	2.10
15–19	81.5	1	0.18	5.56
20–24	798.5	14	2.15	6.51
25–29	1,464.5	20	4.69	4.26
30–34	1,507.0	22	6.03	3.65
35–44	2,713.5	51	17.64	2.89
45–54	1,986.0	45	28.99	1.55
55–64	641.0	24	20.90	1.15
65–74	77.5	3	5.13	0.58

[1] Expected deaths, calculated on the basis of mortality from all causes among white persons in New York City. Mortality in the following years was used to obtain an average for the period through which the life experience of Altro patients passed; 1922, 1923, 1924 and 1933, 1934, 1935.

[2] No significant difference in ratios was present when the male deaths, actual and expected, were adjusted to the female years of life.

TABLE 6

Ratio of actual to expected deaths at each stage among patients admitted to Altro 1915–1939[1]

CLASSIFICATION BY STAGE AT ADMISSION TO ALTRO	YEARS OF LIFE OBSERVED	EXPECTED NUMBER OF DEATHS	ACTUAL NUMBER OF DEATHS	RATIO OF ACTUAL TO EXPECTED DEATHS
All stages	9,210.5	85.71	179	2.09
Minimal	2,574.5	28.97	30	1.04
Moderately advanced	3,691.0	30.75	47	1.53
Advanced	2,945.0	25.41	102	4.01

[1] Expected deaths, calculated on the basis of age-specific mortality from all causes among white persons in New York City. Data from the following years were used to obtain an average for the period through which the life experience of Altro patients passed: 1922, 1923, 1924 and 1933, 1934, 1935.

These are quite favorable ratios for a group of tuberculous patients. Equally high ratios are encountered in the general population among apparently well persons in certain economic and occupational groups.

MORBIDITY DATA

Since pulmonary tuberculosis is a chronic recurrent illness which is disabling for long periods of time, it is important to know how often and at what period

recurrences take place and how much of his time the patient spends curing for such recurrences.

Recurrence is defined as reactivation of tuberculosis with resumption of cure either at home or at an institution. Recurrence rates have been computed for our Altro patients by the life table method.

Chart IV presents these facts related to stage of disease at Altro admission. Only first recurrences are shown (table 7).

The chances of having a breakdown after admission to Altro were found to vary with the stage of disease and the time after admission. At the end of ten

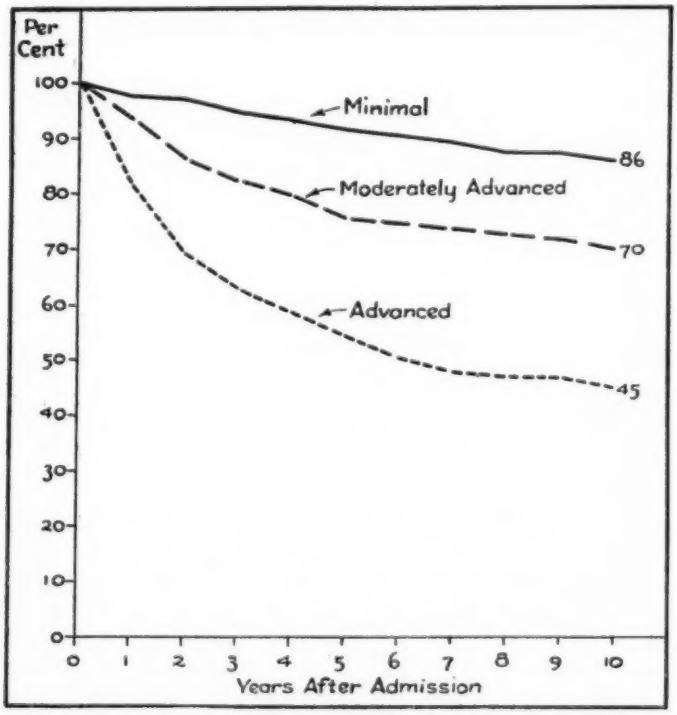


CHART IV. Per cent of patients with no recurrence of illness during ten years after admission to Altro, 1915–1939.

years, 86 per cent of the patients with minimal disease had escaped recurrence, compared with 70 per cent of the patients with moderately advanced disease and only 45 per cent of the far advanced patients.

During the first five years the average annual rate of first recurrence for patients classed as moderately advanced and far advanced was respectively three and seven times the average rate noted among patients with minimal tuberculosis. During the second five years, all the rates were lower as can be seen in the leveling off of the three curves. The lower recurrence rates of the second five-year period are partially conditioned by the fact that only first recurrences are shown.

The next presentation concerns the percentage of time spent curing from all tuberculous illness *following Altro discharge.* The data are given in three five-

TABLE 7

Recurrence of illness from tuberculosis. Patients classified according to stage at Altro admission (1915–1939).

YEARS AFTER ADMISSION TO ALTRO	PERCENTAGE WITH NO RECURRENCE DURING PAST AND SPECIFIED YEARS		
	Minimal	Moderately advanced	Far advanced
0–1	97.51	93.20	81.48
1–2	96.00	86.05	69.21
2–3	94.41	82.07	62.93
3–4	93.30	79.80	58.64
4–5	91.57	75.45	54.11
5–6	90.41	74.43	50.47
6–7	89.19	73.69	47.85
7–8	87.19	72.44	46.85
8–9	87.19	71.49	46.85
9–10	85.78	69.85	44.91

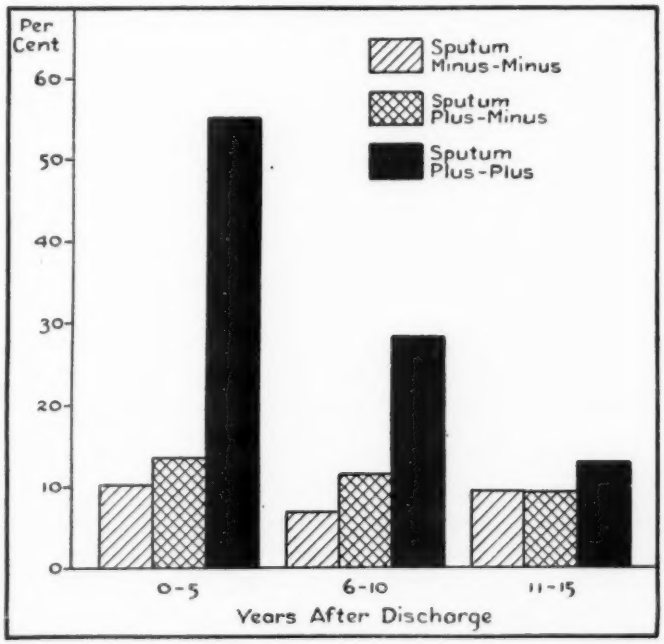


CHART V. Per cent of years alive that were tuberculous sick years post Altro

year periods and are related to the patient's sputum history at Altro admission (chart V and table 8).

The results are striking. The patients of the minus-minus group spent 10

per cent or less of their time in bed in all three five-year periods. The plus-minus patients were quite similar in this respect to the minus-minus group. They spent a slightly greater proportion of their time curing in the first two five-year periods than the patients of the minus-minus group, but in the last period the figures are identical for both groups.

How much worse are the figures for the group of patients who entered the workshop with a positive sputum! In the first five years, these patients were invalided by tuberculosis 55 per cent of the time, four to five times that of the more favorable sputum groups. In the second and third five-year periods, the proportion of sick years spent curing decreased to 28 per cent and 13 per cent, respectively. Since, as previously shown, mortality operated most forcibly upon the plus-plus group of patients in the first five years following Altro dis-

TABLE 8

Per cent of years alive that were tuberculous "sick years" post-Altro. Patients classified according to sputum history at Altro admission

YEARS AFTER DISCHARGE FROM ALTRO	YEARS ALIVE POST-ALTRO	SICK YEARS POST-ALTRO	PER CENT
	Sputum Minus-minus		
1–5	1,282	132	10.3
6–10	965	68	7.0
11–15	313	30	9.6
	Sputum Plus-minus		
1–5	1,939	266	13.7
6–10	699	80	11.4
11–15	321	30	9.3
	Sputum Plus-plus		
1–5	569	314	55.2
6–10	357	101	28.3
11–15	160	21	13.1

charge, thus eliminating the more sickly, the more resistant survivors in the second and third five-year period spent proportionately less time curing. But even in these later periods the plus-plus group of patients never reached the low level of sick years of either the minus-minus group or the plus-minus group.

These data on tuberculous "sick years" post-Altro for different classes of patients represent an important and realistic measure of the net effect of recurrence of illness.

It will be recalled that 85 per cent of all Altro patients were either in the plus-minus or minus-minus sputum group. In these patients, who constitute such a great majority, the percentage of "well years" in each of these three five-year periods following Altro discharge has never fallen below 86 per cent and, in one group, has been as high as 93 per cent. Thus "well years" during which our

patients were productive members of the community make up by far the greatest part of post-Altro life.

CONCLUSIONS

This statistical review of the medical experience of a group of tuberculous patients who underwent a temporary rehabilitation course at the Altro Work Shops during the past quarter century demonstrates that such a scheme is clinically sound. For the record of these patients is satisfactory, as measured by their subsequent mortality, their recurrence rates and the time they lost as a result of these recurrences.

The importance of conversion of sputum and its relation to a favorable prognosis is fully confirmed by this study, since the patients in whom conversion had been achieved before Altro admission had about as low a death rate and lost little more time from recurrence of disease than those patients who never had a positive sputum.

As a nation at war, our tuberculosis problem will assume increasing importance. Rehabilitation can be a most important adjunct in handling it. Expansion of this inadequately developed portion of antituberculosis work is feasible, practicable, necessary, sound.

SUMMARY

1. Nine hundred and sixty-four patients with pulmonary tuberculosis were admitted to the Altro Work Shops, a medically controlled garment factory, for a rehabilitation course between the years 1915–1939, and were followed to the closing date of the survey, July, 1941.

2. The longest period of follow-up medical observation was twenty-five years and the shortest, one and one-half years. Ninety-seven per cent of the patients were traced five years; 92 per cent could be traced ten years.

3. In the earlier period 1915–1929, only 6 per cent of the patients received collapse therapy before Altro admission; in the later period, 1930–1939, 52 per cent had some form of collapse therapy.

4. Four out of 5 patients had moderately advanced or far advanced lesions on entry to the workshop. In 64 per cent of instances the patients' lesions were arrested and 8 per cent were unstable or frankly active. These latter date back to the early experience of the workshop, 1915–1929.

5. Thirty per cent of patients had no record of a positive sputum before admission to the workshop (minus-minus group). Fifty-five per cent had a positive sputum which had been successfully converted to negative sputum before admission to the workshop (plus-minus group). Fifteen per cent still had positive sputum at admission to the workshop (plus-plus group).

6. The percentage of patients with successful sputum conversion before Altro admission (plus-minus group) rose from 38 per cent in the 1915–1929 period to 69 per cent in the 1930–1939 period. The percentage of patients admitted to the workshop with positive sputum (plus-plus group) fell from 25 per cent in the 1915–1929 period to 6 per cent in the 1930–1939 period.

7. At the end of ten years after discharge from Altro, 87 per cent of the patients with minimal lesions and 86 per cent of patients with moderately advanced lesions had survived. For patients with far advanced lesions, the survival was 63 per cent.

8. Patients with successfully converted sputum before Altro admission (plus-minus group), as well as patients who had no record of positive sputum before Altro admission (minus-minus group), were alive in 84 per cent of instances at the end of ten years. Only 54 per cent of those admitted to the workshop with positive sputum (plus-plus group) survived at the end of ten years.

9. For the entire experience, the mortality of Altro patients was about twice that of the general population of the same age and sex composition. The patients with minimal lesions at Altro admission had a death rate which was the same as that of the general population; patients with lesions in the moderately advanced stage at Altro admission had a death rate of one and one-half times that of the general population; and patients with far advanced lesions four times that of the general population.

10. At the end of ten years, 86 per cent of the patients with minimal disease at Altro admission escaped recurrence or breakdown; 70 per cent of the patients with moderately advanced lesions and 45 per cent of patients with far advanced lesions had no recurrence.

11. In the group of patients who had a negative sputum when they were admitted to the Altro Work Shops (85 per cent of the total number) 86 per cent to 93 per cent of their first fifteen years after Altro discharge were spent as "well years."

SUMARIO

1. Novecientos sesenta y cuatro enfermos con tuberculosis pulmonar fueron admitidos en un curso de rehabilitación durante los años 1915–1939 en los Talleres Altro, fábrica de ropa atendida por médicos, siendo observados hasta la fecha en que terminó el estudio, en julio de 1941.

2. El período más prolongado de observación médica fué 25 años y el más breve año y medio. A 97% de los enfermos se les siguió por espacio de cinco años y a 92% por 10 años.

3. En el período más temprano, 1915–1929, sólo 6% de los enfermos habían recibido la colapsoterapia antes de ser admitidos en los Talleres Altro, comparado con 52% en el último período.

4. A su ingreso en los talleres, 4 de cada 5 enfermos mostraban lesiones moderadamente o muy avanzadas. En 64% las lesiones se hallaban estacionadas y en 8% eran inestables o francamente activas, remontándose estos últimos a los primeros tiempos del taller (1915–1929).

5. En 30% de los enfermos no había datos de esputo positivo (grupo menos-menos) antes de su ingreso en los talleres; en 55% había habido esputo positivo que se había transformado en negativo antes de su ingreso (grupo más-menos), y en 15% todavía había esputo positivo al ingresar (grupo más-más).

6. El porcentaje de enfermos en que se negativó el esputo (grupo más-menos)

antes de su ingreso en los Talleres Altro se elevó de 38% en el período 1915–1929 a 69% en el período 1930–1939, mientras que el porcentaje de los de esputo positivo (grupo más-más) disminuyó de 25% en el período 1915–1929 a 6% en el período 1930–1939.

7. A los 10 años del alta de los talleres sobrevivían 87% de los enfermos de lesiones mínimas y 86% de los de lesiones moderadamente avanzadas, mientras que en los que tenían lesiones muy avanzadas la proporción era de 63%.

8. De los enfermos con esputo negativo antes de su ingreso (grupo más-menos) así como de aquéllos en que no había datos de esputo positivo antes (grupos menos-menos) un 84% se hallaban vivos al cabo de 10 años, mientras que sólo sobrevivían 54% de los recibidos con esputo positivo (grupo más-más).

9. Durante todo el período, la mortalidad en los enfermos recibidos en Altro fué aproximadamente el doble que en la población general de la misma composición en cuanto a edad y sexo. En los casos de lesiones mínimas la mortalidad fué idéntica que en la población general, mientras que en los moderadamente avanzados fué una y media veces mayor y en los de lesiones muy avanzadas, cuatro veces mayor.

10. Al cabo de 10 años, 86% de los enfermos con lesiones mínimas a su ingreso no habían experimentado recurrencias o desintegración, comparado con 70% en los de lesiones moderadamente avanzadas y 54% en los de lesiones muy avanzadas.

11. En el grupo de enfermos de esputo negativo a su ingreso en los Talleres Altro (85% del total), 86 a 93% habían pasado los primeros 15 años consecutivos al alta como años sanos.

Acknowledgments: This study was made under a grant from the Nathan Hofheimer Foundation, Inc. Acknowledgments are made to the Milbank Memorial Fund for coöperation in the study through a grant of personnel and facilities and to Miss Jean Downes of the Fund's staff who is responsible for the analysis of the statistical results of the study; to Mrs. Martin Paskus of the Committee for the Care of the Jewish Tuberculous for her aid in the painstaking task of preparing the schedules of our patients.

REFERENCES

(1) Frost, W. H.: Risk of persons in familial contact with pulmonary tuberculosis, Am. Pub. Health, 1933, *23*, 426.

(2) Downes, Jean: A study of mortality among individuals with active pulmonary tuberculosis, Milbank Memorial Fund Quarterly, July, 1938, *16*, No. 5.

(3) Hilleboe, H. E.: Post-sanatorium tuberculosis survival rates in Minnesota, Pub. Health Rep., 1941, No. 56, 895.

(4) Bardswell, N. D., Thompson, J. H. R.: Medical Research Commission of Great Britain, 1933, No. 33.

(5) Life and a Living, The Committee for the Care of the Jewish Tuberculous, Inc., New York, N. Y., 1936.

(6) Siltzbach, L. E.: Rehabilitation of the tuberculous, Am. Rev. Tuberc., 1941, *44*, 357.

DISCUSSION

Dr. Olin S. Pettingill, Middleton, Massachusetts: Doctor Siltzbach has shown what has been accomplished with a well organized and supervised group of tuberculous patients.

It is not necessary to call the attention of this audience to the treacherous nature of pulmonary tuberculosis and the importance of supervising everything that enters into the environment of tuberculous patients, at work and in the home. Eternal vigilance is the price of life and health. I have been interested in what Doctor Siltzbach reports on prognosis of a group of patients who were positive and later converted to negative, compared with patients who never had positive sputum. I am also interested in the expectancy of life in this group of negative sputum cases, compared with the general public. It reminds me of what Doctor Pillsbury once said, "One must have a little tuberculosis in order to be perfectly well."

At Essex Sanatorium, Middleton, Massachusetts, we have been disturbed because a comparatively large number of patients were readmitted each year. During the past ten years there has been an average of 337 patients admitted each year, and of this number, 82 were readmissions; or 24.3 per cent of our cases admitted each year over this period were readmissions of former patients. Of the 82 readmissions during the past ten years, when previously discharged, 31, or 26.2 per cent, left the sanatorium with consent of the medical staff. Obviously, we should not consider as failures of treatment or rehabilitation, patients who left the sanatorium against advice of the medical staff. During this period, the number of readmissions has shown no definite trend, which was expected after extensive use of collapse therapy. There has been an increase in the percentage of patients leaving the sanatorium with negative sputum, from 24 per cent in 1921 to 93 per cent in 1940.

In an effort to reduce this comparatively large number of readmissions, we have established at Essex Sanatorium the following set-up: A full time rehabilitation director takes charge of the occupational activities of the patients. Under, and working with him is a full-time teacher, an occupational therapy director and at various times we have had special teachers. When a patient is admitted to Essex Sanatorium, unless hopelessly ill, his occupational background is investigated and his aptitude determined and he is immediately started in preparation for some form of suitable vocation. We find that this is stimulating to the patient's interest in utilizing his occupational time to advantage.

The rehabilitation director offers guidance to patients and ex-patients in their occupational problems and assists them in securing positions, but he does not maintain an employment bureau. Last year 20 patients were helped in securing suitable occupations and a total of 80 of our discharged patients were satisfactorily employed. We hope, with this set-up, to be able to reduce what seems to us rather a high readmission rate.

CHRONIC PULMONARY TUBERCULOSIS[1]

Clinical and Roentgenological Observations over a Ten-Year Period without Collapse Therapy

H. R. NAYER AND MAX PINNER

Pulmonary tuberculosis is a disease of exquisite chronicity. Over periods of months and years, the multiple facets of the disease, the many changes of progression and retrogression make their appearance side by side with varying tempo and intensity. In order to gain a clear conception of the "natural" course of pulmonary tuberculosis, it is necessary to make serial clinical and X-ray studies over periods of years. Such observations are valuable because of what may be learned from them with regard to the life cycle of the disease and the fundamental processes which underlie all our attempts at active therapy. They may also form a much needed base line for an accurate evaluation of the efficiency of therapeutic procedures. Studies of tuberculosis in the uncollapsed lung have not been frequent and have, for the most part, concerned themselves with observations on the healing of cavities and early infiltrations (1, 2, 3, 4). When collapse therapy is used, the pattern of the disease is altered and the spontaneous changes cannot be clearly seen and often pass unnoticed. With the increasing use of collapse therapy, serial studies of pulmonary tuberculosis without collapse therapy have become even less frequent. The methodical use of serial roentgenography and the more frequent application of collapse measures have developed simultaneously, so that the natural history of the disease which can properly only be evaluated by serial X-ray studies is largely obscured by the progress of modern therapy.

It was, therefore, believed that it would be of interest to review a group of cases, carefully followed over periods of many years, who had not received any treatment except bed-rest. At this institution, we see a relatively large number of middle aged and elderly tuberculous patients in whom collapse therapy is not feasible. In some, the disease is bilateral and very extensive and is not deemed suitable for collapse measures. In others, pneumothorax induction is precluded by an obliterated pleural space and surgical measures are contraindicated because of the extent of the disease, the age of the patient and other medical considerations, such as cardiovascular disease. A number of these patients were first seen at a time when the use of collapse measures was much more restricted than at present. Some have been under observation at Montefiore Hospital and clinic and at the Montefiore Country Sanatorium for periods up to thirty years.

Criteria for selection: One hundred and two patients of the type described above were selected for study. These were all individuals who had pulmonary tuberculosis for ten years or more. The disease had been active or intermittently

[1] From the Division of Pulmonary Diseases, Montefiore Hospital for Chronic Diseases, New York, New York.

active during most of that period and X-ray films going back ten years or more were available. The great majority were followed for more than a decade at this institution. In the remaining few, the early data and roentgenograms were obtained from other institutions. Approximately 700 case records were surveyed before this series was obtained. It should be clearly understood that no attempt has been made to carry out any statistical studies. A sufficiently large group was chosen in order to be able to study the main phases of the disease in the uncollapsed lung but none of the figures used in this study can be used as the basis for statistical conclusions.

There were 66 males and 36 females. The age at clinical onset of the illness and present age are given in tables 1 and 2. The average period of time during

TABLE 1

Distribution of patients according to age at onset of disease

AGE	MALE	FEMALE
10–19	8	10
20–29	13	13
30–39	18	8
40–49	21	3
50–59	5	2
60–69	1	

TABLE 2

Distribution of patients according to age at present

AGE	MALE	FEMALE
20–29	4	2
30–39	7	13
40–49	11	10
50–59	32	6
60–69	10	4
70–79	2	1

which these patients were observed was 12.9 years. The shortest period of regular observation, that is, at approximately yearly intervals, was six years and the longest, thirty-three years. In 99 patients, sufficient data were available for determination of the extent of disease at the time of first diagnosis. There were 6 minimal cases, 48 moderately advanced and 45 far advanced.

It is characteristic of this type of patient that he wanders from sanatorium to sanatorium in search of a cure. Many of them are frequently readmitted to the hospital for intermittent exacerbation or for the sequelae of pulmonary tuberculosis, such as bronchiectasis, emphysema and cardio-respiratory insufficiency. The average period of hospitalization in this group was thirty-three months (table 3).

Owing to this long average hospital stay, almost three years, this type of

patient constitutes one of the most important problems in the field of tuberculosis, taxing the burdened facilities of tuberculosis institutions. When the disease is active, hospitalization is necessary. From table 4 it can be seen that, while patients with a long duration of active disease remain in the hospital for long periods, the period of hospitalization increases considerably less than the period of active disease. Of greater significance, in this regard, is the patient with positive sputum and quiescent disease who is a custodial rather than a hospital problem. Forming a menace to the community, particularly under crowded living conditions, they are frequently sent back to the hospital again and again, even though the disease remains quiescent and nonprogressive. With the increasing number of patients who manifest the first evidence of clinical disease in the older age periods, these people will make up an increasingly

TABLE 3

Time spent in hospitals and sanatoria

PERIOD OF RESIDENCE IN INSTITUTIONS	NUMBER OF PATIENTS
1– 12 months	23
13– 24 months	20
25– 60 months	46
61–120 months	12
144 months	1

TABLE 4

Relation of period of hospitalization to period of active tuberculosis

DURATION OF ACTIVE TUBERCULOSIS	NUMBER OF PATIENTS	AVERAGE DURATION OF HOSPITALIZATION
Up to 1 year	9	13.5 months
2– 5 years	66	27.6 months
6–10 years	17	49.5 months
11–15 years	10	65.8 months

important portion of the sanatorium population until more adequate custodial accommodations can be provided. Some idea of this problem can be gained when an attempt is made to correlate the period of positive sputum with the time spent in institutions (table 5).

If the sixteen to twenty-five year groups in table 5, which comprise but 3 patients, are excluded, it can be calculated that, on the average, these patients were hospitalized for about 70 per cent of the time that the sputum was positive. A number of the patients in this series had quiescent disease with positive sputum for periods up to several years. In the vast majority of patients, the period of hospitalization was considerably shorter than the period of positive sputum; this discrepancy is particularly striking in patients with a long history of positive sputum.

Table 5 also reveals the great variability in the duration of positive sputum

in these patients. In a few of the patients going back many years, early sputum records were not available. In others, there were intermittent periods of negative sputum due to apparent arrest of the disease. When reference is made to sputum-positive periods, this means, in some cases, the total of a number of periods interrupted by sputum-negative intervals.

X-ray classification: The majority of the cases fell into two large groups: those with mainly fibroid disease and those with predominantly cavitary involvement. In the first group were included those who, throughout the major period of observation, presented roentgen evidence of confluent productive disease, either slowly progressive or stationary, without any clear-cut evidence of cavitation. In view of the positive sputum in many of these patients, there were undoubtedly areas of tissue breakdown but these were not sufficiently large to make an X-ray diagnosis of cavity possible. Cavitation appeared in a few of these cases toward the end of observation. There were 35 patients with this type of fibroid disease. In 29, the involvement was bilateral while in 6 the disease remained essentially unilateral.

TABLE 5

Relation of period of hospitalization time to period of positive sputum

PERIOD OF POSITIVE SPUTUM	NUMBER OF PATIENTS	AVERAGE DURATION OF HOSPITALIZATION
0- 1 year	23	19.4 months
2- 5 years	37	32.5 months
6–10 years	18	42.7 months
11–15 years	21	36.0 months
16–20 years	1	29.0 months
21–25 years	2	88.5 months

There were 8 cases which may be listed as a subgroup under the fibroid series. These were examples of bilateral disseminated nodular disease with slow spread in an apico-caudal direction. From the roentgen standpoint, they could be classified as probable cases of chronic haematogenous tuberculosis. Subsequently, in some of these patients, the original picture was modified by various types of bronchogenic spread and cavitation.

At some time during observation, there was X-ray evidence of cavity in 51 patients. In 9 patients, the vomicae, when first observed, could be classified as caseo-cavitary. In these, the cavity wall was somewhat irregular and shaded off, without clear-cut demarcation, into a wide surrounding zone of exudative disease. The remainder were of the fibro-cavitary variety: the cavity wall was usually distinct and regular and was surrounded by strand-like and hard areas of fibrosis. Thus, as far as could be judged from the roentgen picture, the great majority of these cavities were not recent lesions when first discovered. In 26 of these patients, there was persistent cavitary disease, either on one or both sides, throughout the major period of observation.

Cavity closure: In 24 cases there was definite X-ray disappearance of one or

more cavities which remained closed for years under observation. In one patient, a right upper lobe cavity closed while a left upper lobe cavity was being blocked. The sputum became negative after blocking of the left cavity was complete in 1931. Both cavities went on to apparent healing and the patient is now apparently cured. In a second case, a left cavity closed while a right cavity opened and closed intermittently on several occasions. In a third case, in spite of the apparent disappearance of a left upper lobe cavity ten years ago, the sputum has remained positive, probably due to persistent fibroid disease. In the remaining 21 patients, the closure of the cavity coincided with the beginning arrest of the tuberculosis; the sputum became negative and these have all gone on to apparent healing of the disease. Four presented bilateral cavitation. It was not unusual to observe the closure of two or more cavities in the same patient, usually at different times. There was a total of 31 closed cavities in these 24 patients (table 6). Owing to the absence of lateral and oblique X-ray films, it was not possible to ascertain definitely the lobar location of the mid-zone cavities.

In 5 patients two cavities closed and in one case three cavities closed. The cavities ranged in size from 0.6 cm. to 6.5 cm.; the majority ranged from 1.5 cm.

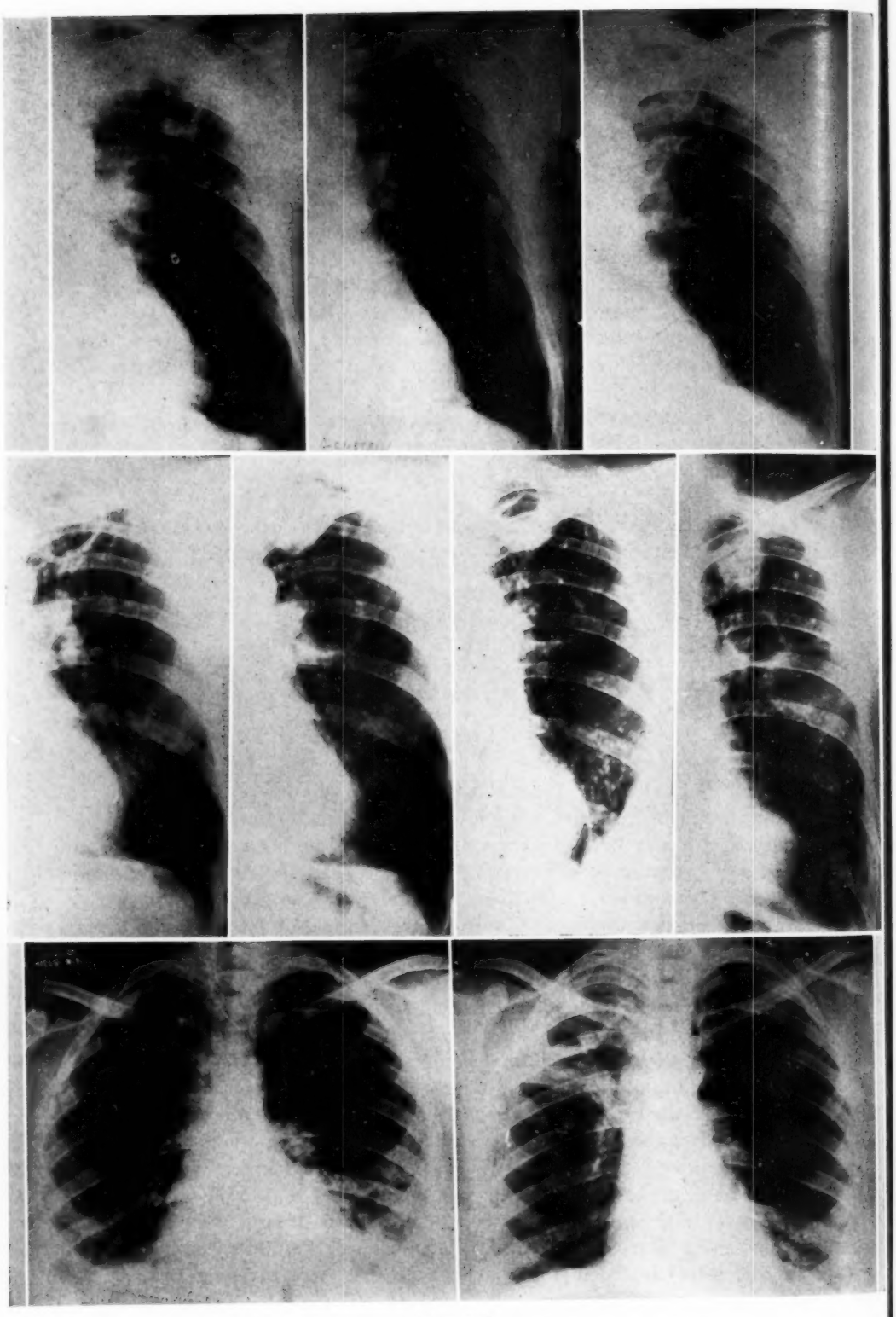
TABLE 6

Data on closed cavities

TYPE OF CAVITY AT FIRST OBSERVATION	NUMBER OF CAVITIES	LOCATION OF CAVITY	NUMBER OF CAVITIES
Fibro-cavitary	25	Left upper lobe	15
Caseo-cavitary	6	Right upper lobe	10
		Mid-zone	6

to 3 cm. in the largest diameter. While a few of the smaller lesions closed within a few months or a year, in most patients the process of closure went on for several years before completion (figures 1, 2, 3). These patients have been followed from three to fourteen years since X-ray disappearance of the cavity. The end-result was an area of fibrosis at the site of the former cavity. In some cases, there was additional calcification. Frequently, one gained the impression of shrinkage in the region of the cavity; in a few there were definite shrinkage and retraction of the entire lobe with displacement of the interlobar fissure.

Blocked cavities: In 3 patients there was evidence of cavity closure by blocking (table 7). Serial X-ray films showed gradual obliteration of the cavity by the accumulation of fluid material until, ultimately, there was a dense round opacity corresponding to the former cavity (figures 4, 5, 6, 7). The process of complete blocking was slow and took from one to four years. In 2 patients the cavities reopened and subsequently were again blocked. The blocked cavities in cases II and III have undergone shrinkage and fibrosis and appear to have healed. In cases I and II the process of cavity blocking has been merely an incident in the clinical course since, at the same time, there has been persistently positive sputum and active disease in other portions of the lungs. In case III the block-



FIGS. 1–9

ing of the cavity, which represented the sole active focus of disease, coincided with clinical arrest of the tuberculosis and the patient has gone on to apparent cure.

Intermittent cavity closure: Five patients illustrated the process of intermittent cavity closure (table 8). Here, the cavities disappeared, for varying periods of time, by apparent collapse and apposition of the walls (figures 10, 11, 12, 13, 14). This process generally occurred rather rapidly and in each case the cavity reopened at least once. On the roentgenogram, the closed cavity was represented by a linear density or several strand-like areas. All the lesions were fibrocavernous in type. In 4 patients, cases A, B, D and E, the intermittent cavity was the sole active focus of disease; in these, the sputum became negative and the tuberculosis was apparently arrested during each period of cavity closure. Case C had bilateral active disease and the sputum remained positive throughout.

In all 5 patients, the cavities increased in size during observation. In case E, following the second cavity closure, the tuberculosis has been apparently cured.

TABLE 7

Data on patients with blocked cavities

CASE	DATE CAVITY DIAGNOSIS	CAVITY DIAMETER	CAVITY LOCATION	DATE FIRST BLOCK	DATE FIRST RE-OPENING	DATE SECOND BLOCK	FOLLOW-UP
		cm.					
I	1932	5	LUL	1934	1937	1940	Remains blocked
II	1929	2.5	RUL	1933	1934	1938	Gradual shrinkage and fibrosis
III	1930	3	LUL	1931			Shrinkage and fibrosis persisting to last observation in 1937

In the remaining patients, the process of intermittent closure has not exerted any beneficial effect upon the course of the illness. One patient has had an

Top row: FIG. 1. Left. Left lung. X-ray film taken April 16, 1929 showing large cavity in mid-zone and smaller cavity in infraclavicular region. FIG. 2. Center. May 25, 1934. The mid-zone cavity is much smaller. The infraclavicular cavity is no longer visible. FIG. 3. Right. March 18, 1940. No cavities are seen. There is some residual fibrosis. The right lung remained essentially negative throughout. Pulmonary disease is arrested.

Center row: FIG. 4. Left. February 24, 1932. Left lung. Large cavity in upper lobe. FIG. 5. Left center. May 1, 1934. Upper lobe cavity is now completely blocked. An other cavity, adjacent to the left hilum, has appeared. FIG. 6. Right center. August 6, 1937. The blocked cavity has partly emptied itself. The hilar cavity persists essentially unchanged. There is a pleural effusion following a spontaneous pneumothorax in 1936. FIG. 7. Right. December 9, 1940. The upper cavity is again completely blocked. The hilar cavity is somewhat smaller. A new large cavity has appeared in the mid-zone just below the hilar cavity. The right lung has remained inactive throughout.

Bottom row: FIG. 8. Left. July 29, 1930. There is a large right upper lobe cavity. There are a few infiltrations in the left lower lobe. FIG. 9. Right. February 6, 1940. The right upper lobe cavity persists. There has been some retraction of the right upper lobe. The left lung has remained essentially negative throughout.

unsuccessful thoracoplasty in 1936 (case D), another (case A) is now undergoing thoracoplasty and cases B and C are apparently hopeless problems with open cavities and progressive disease.

Persistent unilateral disease: One of the most justly feared dangers in pulmonary tuberculosis is the spread of disease from an active focus through the bronchi to uninvolved portions of the lungs. This process is variable and it is not possible to predict when and where a spread will occur. It is generally

TABLE 8

Data on patients with intermittent cavity closure

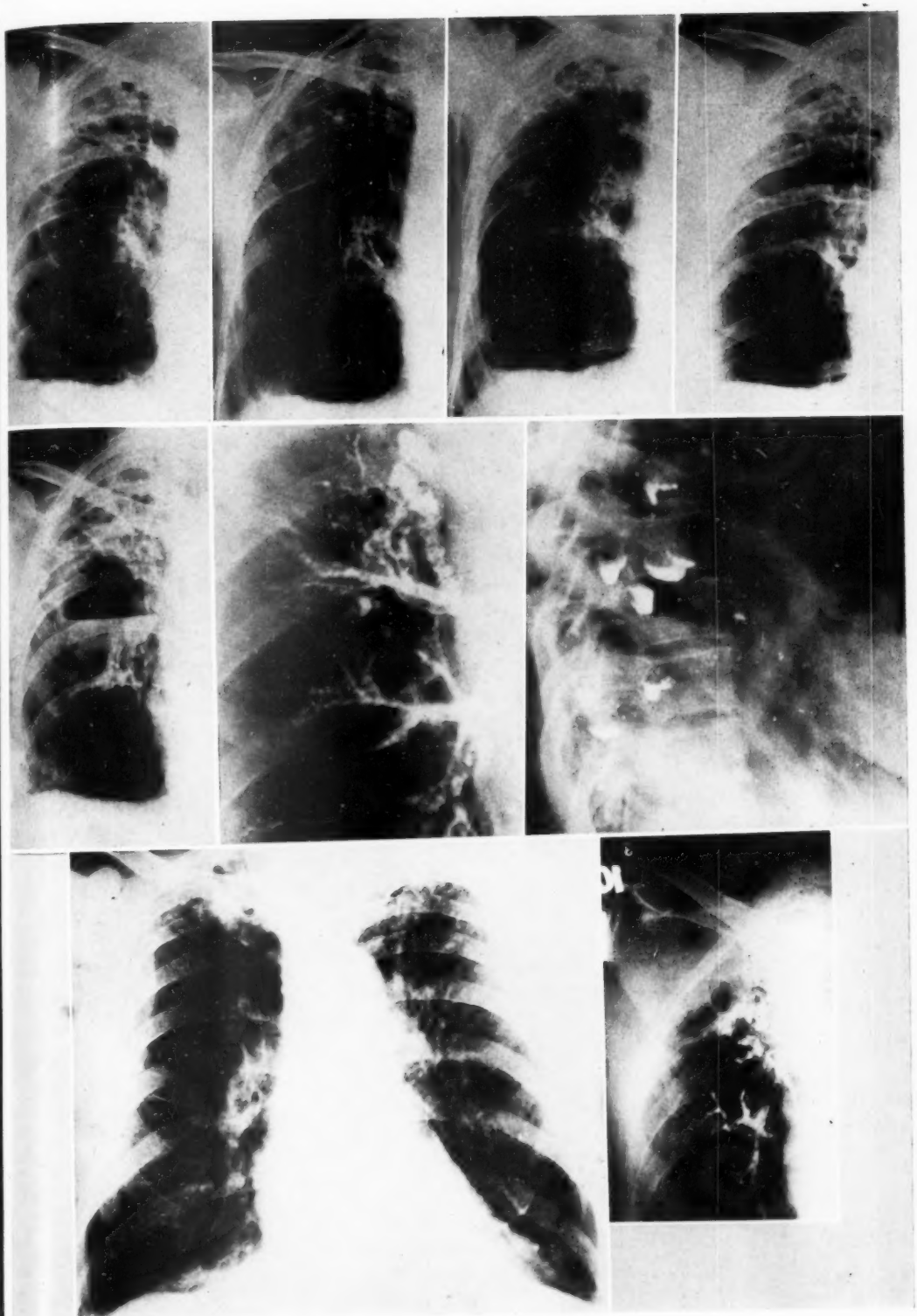
CASE	AGE AT FIRST CAVITY DIAGNOSIS	DATE OF CAVITY DIAGNOSIS	LOCATION OF CAVITY	CAVITY DIAMETER, FIRST DIAGNOSIS	FIRST CLOSURE	FIRST REOPENING	SECOND CLOSURE	SECOND REOPENING	THIRD CLOSURE	CAVITY DIAMETER, LAST OBSERVATION	FOLLOW-UP
				cm.						*cm.*	
A	20	1923	LUL	2	1930	April 1935	Dec. 1935	1939		5	Undergoing thoracoplasty. Sputum positive
B	39	1930	Right mid-zone	2	1933	1934	1936	Feb. 1938	Dec. 1938	6	Cavity reopened in 1940
C	51	1931	Left mid-zone	2	1934	1935	1937	1938		7.5	Cavity remains open
D	16	1924	RUL	2.5	1926	1932				6	Remained open. Thoracoplasty in 1936. Sputum positive
E	34	1927	RUL	4	Sept. 1928	Dec. 1928	1930			4.5	Remains closed. Sputum negative. Last follow-up in 1940

true that the longer the period of positive sputum, the greater are the chances of intrabronchial spread. How unpredictable this problem of spread can be is

Top row: FIG. 10. Left. November 27, 1935. Right lung. Large mid-zone cavity which appeared suddenly and ballooned out as if under tension. FIG. 11. Left center. September 12, 1936. The cavity has disappeared. Sputum became negative. FIG. 12. Right center. February 9, 1938. The cavity has reappeared. FIG. 13. Right. December 15, 1938. The cavity has disappeared again. Sputum again became negative.

Center row: FIG. 14. Left. February 29, 1940. The cavity has reopened and a fluid level is now present. FIG. 15. Center. Lipiodol bronchogram showing ectatic right upper lobe bronchi. FIG. 16. Right. Lipiodol bronchogram of right lung showing saccular ectasia.

Bottom row: FIG. 17. Left. Film shows upper lobe fibrosis with marked lower lobe emphysema and bulla formation. FIG. 18. Right. Lipiodol bronchogram showing right upper lobe bronchiectasis.



FIGS. 10–18

illustrated by 12 patients in this group. They were all patients with extensive disease and richly bacillary sputum in which the involvement remained essentially unilateral for periods of many years (figures 8, 9). Sputum measurements were not available but it is known that all these patients were coughing and bringing up sputum. Eleven had cavitary disease and one had fibroid involvement. The periods of positive sputum ranged from five to fifteen years; 8 of the 12 patients had positive sputum for ten or more years. In some, a few scattered tubercles appeared on the contralateral side but these either resorbed or remained stationary. It is reasonable to assume that, during the course of years, these patients aspirated numerous bacilli into various portions of both lungs, yet the disease remained unilateral.

The factors involved in bronchogenic spread are multiple and, in all probability, both mechanical and immunological processes play a rôle. Some of these factors may be mentioned here. The quantity of the sputum is of some importance in this regard. Where the sputum is profuse, the opportunity for spread would appear to be greater. Further, when the sputum is very fluid, it is more easily aspirated into the finer pulmonary divisions, as contrasted to thicker gelatinous secretion. The various modifications of the cough reflex, observed in tuberculous patients, are also to be considered. The enfeebled patient is often physically unable to cough up all the sputum which has reached the larger bronchi; consequently, there is much retained bacillary sputum with resulting greater opportunity for aspiration into uninvolved portions of the lungs. The patient with paroxysmal type of cough is often forced to halt for breath before he has cleared his larger bronchi; during this halt, which is followed by a forceful prolonged inspiration, the retained sputum may be spread to various portions of the lungs. This paroxysmal irritative type of cough is not infrequently observed in patients with bronchial lesions. The reasons for the failure to spread in our 12 patients are not clear.

Sequelae of healed pulmonary tuberculosis: During the healing of a tuberculous lesion, except of small exudative foci, there is usually seen a varying amount of fibrosis and distortion of surrounding structures. In extensive lesions, particularly of the cavitary type, the process of healing entails extensive fibrosis and associated shrinkage and distortion of large parts of the lungs and bronchi in order to close the cavity. Mediastinal distortion and retraction frequently accompany these extensive pulmonary changes. This is a slow process; there is usually time for fixation of the mediastinum and significant symptoms rarely result. The pulmonary sequelae of healed tuberculosis, however, are often of clinical significance. Anatomically, these sequelae consist of fibrosis, bronchiectasis, emphysema, pleural obliteration and calcification.

The bronchiectasis occurs in the area of fibrosis; consequently, as Rubin and Newman (5) have pointed out, bronchiectasis of the upper lobes is, in the majority of cases, the result of healed tuberculosis. The emphysema is, in large part, a reaction of compensation of the uninvolved portions of lung. The appearance of symptoms depends to a large degree on the extent of involvement. It is clear that extensive fibrosis and emphysema will result in diminished pul-

monary function with resulting dyspnoea. The great importance of pleural obliteration in the production of diminished pulmonary function has recently been demonstrated by bronchospirographic studies (6).

Bronchiectasis may produce no symptoms. On the other hand, when infection is present, active bronchiectasis with cough and expectoration of large amounts of sputum, sometimes foetid, dominates the clinical picture. These signs of activity usually indicate bronchiectatic involvement of the lower as well as the upper lobes, since profuse sputum, foetid breath, clubbing of fingers, etc. are unusual when the upper lobes alone are involved, probably due to better drainage from the upper lobes (5). Haemorrhage, up to alarming amounts, is not infrequently associated with dry upper lobe bronchiectasis. Profuse haemorrhage may result from bronchial erosion by a calcified tuberculous lymph node; in recent years, with more wide-spread use of the bronchoscope, there has been increasing recognition of the significance of this mechanism (7, 8, 9).

In this series, there were 13 patients in whom the tuberculosis had apparently healed but who were left with clinically significant pulmonary symptoms and pathological changes in the lungs. Eight suffered primarily from bronchiectasis and 5 from fibrosis and emphysema. One of these, with extensive bronchiectasis, developed terminal right heart failure; at postmortem examination, there was marked right-sided cardiac hypertrophy and dilatation. Three cases of healed tuberculosis, 2 with bronchiectasis and one with pulmonary fibrosis, manifested no clinically significant symptoms. The following case records were selected to illustrate the various manifestations of these post-tuberculous sequelae.

Case 1: G. D., a fifty-eight year old female whose pulmonary symptoms began in 1906 with haemoptysis. Chest roentgenograms going back to 1925 show bilateral upper lobe fibrosis. Sputum has been negative for fifteen years and the tuberculosis is apparently healed. Frequent blood streaking and occasional larger haemoptyses have necessitated several periods of hospitalization. In the interim, she is able to do some housework although she complains of mild dyspnoea and has a slight cough with moderate nonfoetid sputum. Right upper lobe bronchiectasis has been confirmed by lipiodol injection (figure 15). This patient is a typical example of post-tuberculous upper lobe bronchiectasis with bleeding as the dominant symptom.

The following patient illustrates a more advanced type of bronchiectasis with lower lobe involvement and infection.

Case 2: A. K., a sixty-one year old female whose tuberculosis was diagnosed in 1920. At that time she had bilateral pulmonary disease with right upper lobe cavity. The cavity persisted up to 1932 when it closed, the sputum became negative and the tuberculosis apparently healed. Subsequently, there were several hospitalizations for haemoptysis and dyspnoea. Beginning in 1933, chest X-ray films showed gradual shrinkage and increasing opacity of the right lung. In 1935 cough became severe and there began profuse expectoration of foul sputum not relieved by X-ray therapy. Bronchograms revealed saccular ectasia throughout the right lung (figure 16).

Patient died in 1937 of a bronchopneumonia. At necropsy, the left lung showed almost complete pneumonic consolidation. At the extreme apex there was a puckered anthracotic scar which contained some calcium. The left pleural space was free. The

right lung was markedly shrunken and covered by a thickened, completely adherent pleura. The entire lung was converted into a large number of cavities lined by a fairly smooth membrane and filled with thick pus. These cavities were separated by thick anthracotic fibrous walls. Some of the cavities communicated with bronchi; in others, no bronchial communication was found. Microscopical examination revealed scattered areas of pneumonia in the left lung. Throughout the right lung there were extensive fibrosis, hyalinization, suppurative bronchiectasis and oedema. There was no evidence of specific tuberculous changes in any of the sections.

Case 3: S. G., a fifty-six year old male who developed pulmonary tuberculosis in 1918. He improved on a sanatorium regimen and was well until 1920 when the tuberculosis again became active. Once more the disease was arrested but was reactivated in 1933. On bed-rest the disease became inactive and has remained so, although an occasional positive sputum was obtained up to 1938. Beginning in 1938, he has suffered increasingly from dyspnoea, cough with little sputum and occasional episodes of asthmatic crises. During 1939 there occurred two episodes of right-sided spontaneous pneumothorax, both of which absorbed without complications. It was believed that these were due to rupture of emphysematous blebs. Roentgenograms throughout have shown bilateral upper lobe productive disease with increasing fibrosis and lower lobe emphysema (figure 17).

The following case record illustrates the fact that post-tuberculous changes may exist without producing any significant pulmonary symptoms.

Case 4: M. K., a fifty-one year old male in whom pulmonary tuberculosis was discovered in 1922. The disease remained quiescent until 1932 when active laryngeal involvement was discovered. The laryngeal tuberculosis healed and the pulmonary lesions became inactive. In 1935 Pott's disease was discovered and treated by fusion. Chest X-ray films show a bilateral nodular productive involvement suggestive of haematogenous dissemination; these lesions have undergone increasing fibrosis. Sputum has remained negative and the pulmonary disease inactive. A bronchogram in 1935 disclosed saccular ectasia of the right upper lobe bronchi (figure 18). Aside from minimal cough, there have been no pulmonary symptoms for years.

Present status of patients: The majority of patients passed through various phases of their illness, exemplifying the continually changing pattern of healing and progression. As an illustration, one case of a thirty-seven year old female may be cited. Her illness began at the age of nineteen and she was followed for eighteen years. When first diagnosed, her disease was bilateral with a left upper lobe cavity which closed spontaneously on two occasions and finally remained open. During this entire period, using the National Tuberculosis Association standards, her pulmonary disease was active from 1922 to 1928, quiescent from 1928 to 1933, active from 1933 to 1935, arrested from 1935 to 1939 and active from 1939 to the present. The status of the patients at the end of this study is shown in table 9.

Working capacity: An attempt has been made to determine the functional capacity of these patients in carrying out the ordinary activities of every day life. An admittedly crude classification has been set up, but it was felt that

sufficient information could be obtained for practical purposes. "Good" function implies the ability to perform a full day's work and is equivalent to the working capacity of a fully rehabilitated patient. Patients with "fair" function are able to do only part-time work or to work only under sheltered conditions. Those with "poor" function are unable to do any work and are chronic invalids; some of these are still in the hospital. Function has been correlated with the status of the pulmonary disease in table 9. Eight patients with fair function and 6 with poor function have been listed as apparently cured. This is not strictly in accord with the National Tuberculosis Association standards which require that apparently cured patients be able to carry on under ordinary conditions of life. These patients have been so listed, however, to indicate that their tuberculosis is healed by all criteria, such as negative sputum for two or more years, apparently healed lesions, etc. with the exception of working capacity; all pulmonary symptoms manifested by these patients were not due to tuberculosis but to the changes resulting from healed disease.

TABLE 9

Relation between work capacity and status of disease

STATUS OF LUNG DISEASE	NUMBER OF PATIENTS	GOOD FUNCTION	FAIR FUNCTION	POOR FUNCTION
Active	30		7	23
Quiescent	22	1	10	11
Apparently arrested	3	1	1	1
Arrested	8	5	2	1
Apparently cured	30	16	8	6

From table 9 it can be seen that there is a general direct relationship between working capacity and arrest and healing of the tuberculosis. However, of the apparently cured cases, almost half are unable to do a full day's work and 6 (20 per cent) are unable to work at all. In these patients the tuberculosis has healed, but they are now suffering from the sequelae of the healing, such as dyspnoea caused by fibrosis and emphysema and upper lobe bronchiectasis with haemoptysis and secondary infection. In many patients, onset of poor function coincided with symptomatic onset of the disease. In others, particularly those suffering from post-tuberculous sequelae, the interval between onset of disease and onset of poor function was sometimes a matter of many years. The maximum duration of poor function since onset of the disease was twenty-four years and the minimum was two years; the mean duration was ten years.

DISCUSSION

In the foregoing study, an attempt has been made to illustrate the natural history of pulmonary tuberculosis as manifested in a group of patients with active disease for long periods of time. Particular attention has been paid to the various manifestations of healing uninfluenced by collapse measures.

In this connection, the various types of cavity closure, as observed in this

series, deserve further comment. In those cavities which closed and remained closed, the outstanding features were the slowness of the process and the major rôle played by fibrosis with resulting retraction of the surrounding lung, as observed on the roentgenogram. When the cavity was large, the extensive fibrosis and retraction involved in closing this defect frequently led to marked distortion of the entire lobe. When this was coupled with compensatory emphysema of the remaining lung tissue, the end-result was, not infrequently, a marked impairment of the function of the entire lung. Many of the smaller cavities, on the other hand, healed with little or no apparent significant damage to the lung as a whole. With regard to the mechanism involved in the definitive closure of cavities, no sharp conclusions can be drawn on the basis of our observations. The gradual closure and the obvious rôle of fibrosis and retraction would speak for healing by granulation tissue and scarring, at least in cavities not subjected to collapse measures. This contrasts with the rapid changes frequently seen in cavities where there is evidence that a bronchial mechanism is involved.

The blocked cavity presents a different problem. Several investigators (10, 11, 12, 13) have called attention to the significance of narrowed or closed bronchi in an attempt to explain the mechanism of blocked cavities. According to this explanation, closure or narrowing of the draining bronchi will produce blocking in cavities which already contain a good deal of caseous material which cannot be discharged. Auerbach and Green (13) have stated that bronchial closure will produce cavity closure with scar formation or cavity blocking depending upon a number of factors such as thickness of the cavity wall, vascularity of the cavity wall, the amount of caseation in the cavity wall and the state of the surrounding tissue. Salkin *et al.* (14) have stressed the importance of the cavity wall itself as an active factor in determining the gaseous and liquid content and the pressure within the cavity; these authors believe that a certain number of blocked cavities may occur without the presence of bronchial closure. The influence of bronchial changes upon intracavitary pressures, with particular reference to the check-valve mechanism, has been directly demonstrated by studies following cavity needling and transpleural decompression (12, 15). Brunn *et al.* (15) have shown that the changes in the bronchi leading to the cavity may be reversible and have suggested that this might be explained by allergic inflammation. In one of our patients with a left upper lobe blocked cavity, bronchoscopy revealed a narrowed left upper lobe bronchus; the other 2 were not bronchoscoped.

Cavity closure by blocking cannot always be relied upon to result in healing of the disease. The block may disappear, even after years, with discharge of some of the contents and reopening of the cavity. This was observed in 2 patients in our group. Pinner (16) has pointed out that the blocked cavity is really an intrapulmonary cold abscess.

Intermittent closure of the bronchus or bronchi leading into the cavity would appear to be the most reasonable explanation for the phenomenon of intermittent closure of cavities. The rapid disappearance and equally rapid reopening of

some of these lesions are in favor of this assumption. In the patient who demonstrated opening and closing of a right mid-lung cavity on three different occasions, there was one episode of sudden marked ballooning of the cavity; this could best be explained on the basis of a temporary check-valve mechanism. It is apparent that, at least for a time, the bronchial closure is reversible. Ultimately, either by inspissation of a caseous plug or irreversible inflammatory changes, the obstruction may become permanent and the cavity may go on to healing.

As with the blocked cavities, the prognosis in these cases must be guarded. A cavity which closes rapidly may reopen just as rapidly with further progression of the disease. It has been shown in our 5 cases that, in spite of the periods of closure, the cavities all increased in size. This can probably be accounted for, in some patients, by increased intracavitary pressure resulting from the development of a bronchial check-valve mechanism. However, in others, there appears to be definite progression of the disease.

A strictly clinical and roentgenological study, such as this, can adduce but circumstantial evidence in regard to the mechanism of cavity healing. As has been pointed out in our previous publications, the number of fully observed cavity closures that include a complete pathological examination is still so small that it would appear wiser to defer definite theories on this subject until a broader material is available.

A word of warning must be repeated here. Although cavity closure was observed in 24 out of 102 patients, the reader should not conclude that cavity closure may be expected in more than 20 per cent of patients with advanced chronic pulmonary tuberculosis. The group of patients presented here is strictly selected, not only from the some 700 records examined, as mentioned, but in fact from thousands of records, most of which could not be considered because the patients had not survived a sufficiently long time of observation or because they had been treated by collapse procedures. Our data do not permit, and were not collected with the purpose of establishing the frequency of spontaneous cavity closure.

The anatomical and symptomatic sequelae of healed tuberculosis were particularly striking in this series. It has been shown that almost half of the healed cases were unable to do a full day's work and 20 per cent were unable to work at all. Thirteen were suffering from clinically significant symptoms such as haemoptysis, cough, sputum and dyspnoea. All of these patients had extensive pulmonary tuberculosis. MacMillan (17) has suggested that the process whereby the body is rid of the tuberculous infection is analogous to the healing of acute infections and he has referred to it as "tuberculo-asepsis."

Occasionally, a patient may first come under medical observation only because of symptoms resulting from these post-tuberculous changes. In these cases, the previous existence of tuberculosis can sometimes be inferred from a careful history and particularly from an awareness of the end-results of healed pulmonary tuberculosis. It is reasonable to assume that, in some of these chronic pulmonary cases, the existence of a previous tuberculosis has not been realized.

Thus, although the tuberculosis is healed, the sequelae of this healing may produce symptoms which either continue the chronic invalidism of the patient or may, of themselves, force invalidism on an individual whose function was previously not poor.

In regard to healing pulmonary tuberculosis, it is impressive to see how frequently healing processes occur simultaneously with progressive and destructive disease in the same lung. This leads to one obvious conclusion, namely, that factors of constitutional significance, such as allergy, immunity and hereditary resistance, cannot possibly be of exclusive importance in determining the course of tuberculosis. Strictly local factors, such as "the accident of localization" (Krause), mechanical conditions, congenital and acquired structural peculiarities (and probably many more), must play a significant rôle. In any case, it is a clear demonstration of the futility of all the many attempts to explain the pathological developments of tuberculosis exclusively or mainly on the basis of one factor.

The healing of advanced pulmonary tuberculosis is a painful process. Not only does it entail long illness, but frequently it results in severe anatomical and functional crippling of the involved organ. As pointed out, the functional impairment caused by a healed lesion is not infrequently greater than that of an active lesion. This, parenthetically, is true for healing without and with collapse therapy.

One patient in the entire series developed right heart failure shortly before he died. At autopsy, there was marked right sided cardiac hypertrophy and dilatation. It is probable that there were some patients in this group with right sided cardiac hypertrophy who did not, however, go into failure. However, this was not sufficiently marked to be evident on the routine chest films and cardiac fluoroscopy had not been carried out. Cardiac failure in cases of pulmonary tuberculosis with *cor pulmonale* is usually a terminal phenomenon (18). Only 9 patients in this series were dead at the end of the study; therefore, no conclusions can be drawn with respect to the incidence of clinical cardiac failure. It is clear, however, from this study that these patients, with chronic productive, extensive, bilateral pulmonary tuberculosis with increasing fibrosis, may go on for periods up to thirty years without developing significant cardiac symptoms.

In 71 patients, with extensive bilateral pulmonary tuberculosis, who came to autopsy in one year, Nemet and Rosenblatt (18) have reported that 33 (46.5 per cent) showed right ventricular hypertrophy in association with other hypertrophy and 33.8 per cent showed right ventricular hypertrophy alone. This hypertrophy, determined by measurement of the ventricular wall, was not excessive in any instance. Eleven cases developed terminal cardiac failure. Other causes for this hypertrophy were ruled out. Despite the enlargement of the right ventricle, these authors found that the hearts, in general, were smaller than normal. Ackerman and Kasuga (19), on the other hand, have reported the incidence of right-sided cardiac hypertrophy with marked failure to be low in uncomplicated pulmonary tuberculosis. These authors believe that right-sided hypertrophy without failure occurs in about 6 per cent of all patients who

die of pulmonary tuberculosis. In 330 autopsied cases of pulmonary tuberculosis, they found 53 (16 per cent) instances of chronic *cor pulmonale*. Twenty cases had no evidence of failure. Excluding the cases of failure associated with intrinsic heart disease, there were 21 patients with failure; of these, only 2 had profound failure and 19 had minimal failure of little clinical significance.

It should be mentioned that our patients were a highly selected group from one standpoint. The majority of patients in this institution are Jewish and this is reflected in this group which included 98 Jews and 4 non-Jews. There has been much discussion and disagreement with regard to the manifestations and course of tuberculosis in various national and racial groups. The term "Jewish tuberculosis" is occasionally used to describe the most chronic form of the disease seen in some Jewish patients. The belief that there is actually such an entity as "Jewish tuberculosis" is largely based on clinical impressions and the question as to whether this impression is really true remains open. The material included in this study did not permit us to draw any conclusions in this regard.

There were two facts which seemed outstanding in this study. The first was the remarkable chronicity of the disease as observed in these patients. Although there were periods of quiescence, this chronicity did not imply a static situation. In many of these patients, over periods as long as fifteen and twenty years, there was almost constant movement of the disease process, albeit very gradual. Progression and retrogression frequently went on side by side; one cavity would slowly close over a long period while another made its appearance in the same lung. Secondly, we were constantly impressed by the unpredictability of the disease once the process was well established. Throughout the study, it was well nigh impossible to give an accurate prognosis from the early films and clinical status. Large cavities which appeared hopeless went on to complete healing. Patients with extensive bilateral disease, in whom it appeared hazardous to assume that they would be alive within a year or two, were well and working fifteen years later. On the other hand, patients who appeared well on the road to clinical healing ended up with hopeless progressive disease; this was particularly true of the cases with intermittent cavity closure. Throughout, the picture was one of a chronic intermittent process with numerous phases of activity, quiescence and healing and with one phase shading off into the other.

SUMMARY

1. A group of 102 patients, with active or intermittently active pulmonary tuberculosis, for ten years or more, who have not been subjected to any collapse therapy, has been surveyed.

2. According to roentgenological criteria, these cases could be divided into fibroid and cavitary groups.

3. Three types of cavity closure were observed: definitive closure with healing, blocking and intermittent closure. These are separately discussed.

4. The various sequelae of healed pulmonary tuberculosis are described and illustrated.

5. Outstanding in this group of patients were the remarkable chronicity of the disease, the frequency with which simultaneous healing and progression occurred and the unpredictability of the process once it was well established.

SUMARIO

1. Este estudio comprende un grupo de 102 enfermos que habían padecido constante o intermitentemente de tuberculosis pulmonar activa por espacio de diez años o más, y no habían sido objeto de la colapso terapia.

2. Conforme a las pautas roentgenológicas, estos casos podrían ser divididos en fibroideos y carvernosos.

3. Observáronse tres formas de cierre de las cavernas: cierre definitivo con cicatrización, bloqueo y cierre intermitente. Las tres formas son discutidas por separado.

4. Descríbense e ilústranse con casos, las varias secuelas de la tuberculosis pulmonar curada.

5. En este grupo de enfermos destacáronse: la notable cronicidad del mal, la frecuencia con que se presentaron simultáneamente curación y agravación y la imposibilidad de predecir la marcha una vez establecido el proceso.

REFERENCES

(1) Amberson, J. Burns, Jr.: The roentgenographic pathology of pulmonary tuberculosis, Am. Rev. Tuberc., 1921, *5*, 1.

(2) Amberson, J. Burns, Jr.: Clinical studies of the healing of pulmonary tuberculosis, I. The absorption of pulmonary deposits, Ibid., 1924, *10*, 227.

(3) Jaquerod (Leysin): Spéléologie pulmonaire, Étude clinique et radiologique des cavernes tuberculeuses, Masson et Cie., 1928.

(4) Pottenger, F. M.: Healing of tuberculosis, Ann. Int. Med., 1930, *4*, 281.

(5) Rubin, E. H., and Newman, H. S.: Upper lobe bronchiectasis, Am. J. M. Sc., 1933, *186*, 650.

(6) Pinner, M., Leiner, G., and Zavod, W. A.: Bronchospirography, III. Functional capacity of normal lungs, severely damaged lungs, lungs with strictly parenchymal lesions, thoracoplasty lungs and reëxpanded pneumothorax lungs, J. Thoracic. Surg., 1942, *11*, 241.

(7) Arnstein, A.: Über indurierende Bronchialdrüsentuberkulose als Ursache schwerer Hämaptoe bei älteren Leute, Beitr. z. Klin. d. Tuberk., 1931, *78*, 55.

(8) Vinson, P. P., and Toone, E. C.: Pulmonary symptoms resulting from ulceration of hilar nodes into a bronchus, West Virginia M. J., 1937, *33*, 200.

(9) Cohen, A. G., and Wessler, H.: Clinical recognition of tuberculosis of the major bronchi, Arch. Int. Med., 1939, *63*, 1132.

(10) Eloesser, L.: Bronchial stenosis in pulmonary tuberculosis, Am. Rev. Tuberc., 1934, *30*, 123.

(11) Coryllos, P. N.: The mechanism and biology of tuberculous cavities, Ibid., 1936, *33*, 639.

(12) Eloesser, L.: Blocked cavities in pulmonary tuberculosis, J. Thoracic. Surg., 1937, *7*, 1.

(13) Auerbach, O., and Green, H.: The pathology of clinically healed cavities, Am. Rev. Tuberc., 1940, *42*, 707.

(14) Salkin, D., Cadden, A. V., and McIndoe, R. B.: The blocked pulmonary cavity, Ibid., 1936, *34*, 634.

(15) Brunn, H., Shipman, S., Goldman, A., and Ackerman, L.: Tuberculous cavitation and transpleural decompression, J. Thoracic. Surg., 1941, *10*, 985.
(16) Pinner, M.: Healing of tuberculous cavities, Am. Rev. Tuberc., 1940, *42*, 731.
(17) MacMillan, J. M.: Disappearance of tubercle in pulmonary tuberculosis, Ibid., 1940, *42*, 699.
(18) Nemet, G., and Rosenblatt, M. B.: Cardiac failure secondary to chronic pulmonary tuberculosis, Ibid., 1937, *35*, 713.
(19) Ackerman, L. V., and Kasuga, K.: Chronic cor pulmonale, Ibid., 1941, *43*, 11.

BRONCHIAL OBSTRUCTION AND PULMONARY ATELECTASIS[1]

As Seen in Childhood Tuberculosis with Secondary Bronchiectasis as a Sequela

EDWARD M. KENT[2]

The incidence of pulmonary atelectasis during the course of childhood tuberculosis has been recognized in recent years, and the literature contains confirmatory evidence of this complication from several sources. There are those who have become convinced that the massive roentgenographic shadow, commonly diagnosed as epituberculous pneumonia, is in reality an atelectasis which may involve an entire lung, one or more lobes or a part of any lobe (1, 2, 3).

The bronchial obstruction can be of two general types, namely, the result of intrinsic tuberculous processes within the wall of the bronchus and of compression of the wall of the bronchus from without, notably as a result of increase in size of adjacent lymph nodes. Marked enlargement of peribronchial and hilar lymph nodes is common in childhood tuberculosis.

A few years ago Roessle (1) reported a group of 8 cases which had been diagnosed as tuberculous pneumonia but which he had shown to be instances of atelectasis. The majority of these cases were examples of bronchial obstruction by pressure from enlarged, caseated lymph nodes. In these cases, called "clean" by Roessle, the massive shadow had appeared gradually and subsequent complete anatomical healing resulted. In a minority of Roessle's cases, called "unclean" by the author, perforation of a lymph node into a bronchus was followed by tuberculous lesions within the atelectatic parenchyma. The ideal result of complete healing was not anticipated by Roessle in these latter cases which develop atelectasis as a result of perforation of a caseated lymph node into the bronchus to be followed by tuberculous endobronchitis.

A group of cases of pulmonary atelectasis in patients with childhood tuberculosis comprises the material upon which this study has been based. These 10 cases were in the hospital at the same time, and they were part of the clinical material in the children's wards where a daily census of 85 to 90 cases of childhood tuberculosis is maintained.

The principal objective of this clinical problem has been an effort to determine whether bronchiectasis can be shown to be a sequela of pulmonary atelectasis occurring in the course of childhood type tuberculosis. A secondary objective is to add evidence to the contention that pulmonary atelectasis does occur during the course of childhood tuberculosis and that such cases do represent clinical pictures commonly but erroneously considered to have been instances of epituberculous pneumonia.

CASE SUMMARIES

Case 1: J. T., a Negro female, present age ten years. This child was admitted to the hospital with clinical and roentgenological evidence (figure 1A) of an atelectasis of the left

[1] From the Surgical Service, Glenn Dale Sanatorium for the District of Columbia, Glenn Dale, Maryland.

[2] The Chest Service, Barnes Hospital, St. Louis, Missouri.

upper lobe. In addition there was a serous peritonitis, probably tuberculous. The patient was not particularly ill as a result of the pulmonary atelectasis. Six months later, both clinical and X-ray evidence of definite clearing of the left upper lobe was present. One year after admission the evidence of clearing with aeration of the left upper lobe was more advanced and a bronchogram (figure 1B) prepared at this time revealed distinct bronchiectasis in the previously atelectatic lobe. There is no clinical evidence of infection of the bronchiectasis.

Case 2: W. W., a Negro male, present age four and one-half years. Upon admission to the hospital there were clinical and X-ray (figure 2A) evidences of an atelectasis of the right upper lobe. The history revealed that this child had been quite ill for ten weeks before admission and a diagnosis of tuberculous pneumonia had been made before he was referred for hospitalization. During his hospital residence he has not been materially affected by the pulmonary changes. Laminographic studies of the lungs were made one year after admission and small, cylindrical shadows were shown, which were believed to represent dilated bronchi (figure 2B). Over a period of three years the right upper lobe has gradually contracted so that it now occupies a wedge-shaped area (figure 2C) at the apex and along the mediastinum. The bronchus to this retracted lobe is now open and bronchiectasis is present (figure 2C). There are, in addition, bronchiectatic changes in the midlung field and lateral chest plates revealed this area to be that occupied by the apex of the lower lobe. It is conceivable that the tributary bronchus to this pulmonary segment was occluded at one time during the process. Bronchoscopic examination reveals purulent secretions coming from the right upper lobe, but there is no clinical evidence of marked infection in the bronchiectatic areas.

Case 3: B. V., a Negro female, present age three and one-half years. Upon admission to the hospital there were clinical and roentgenographic (figure 3A) evidences of an atelectasis of the right upper lobe. Although this child was not materially affected by this complication, she had persistent wheezing, rhonchi and musical râles on expiration. Fourteen months after admission the right upper lobe was well aerated and three months later bronchography revealed bronchiectasis in the right upper lobe (figure 3B).

Case 4: S. R., a Negro male, present age six years. This patient was admitted to the hospital with clinical and X-ray evidences of an atelectasis of the left lower lobe. There was a history of acute illness for several weeks previous to entry into this hospital, and a gastric lavage revealed acid-fast bacilli. Four months after admission there was a three-week episode of high fever which subsided after three days of sulfanilamide therapy and there has been no recurrence of a similar bout. Wheezes, rhonchi and musical expiratory râles were present during the obstructive stage of the disease. Twenty months after admission the atelectasis had resolved. This patient is the single instance of appreciable mediastinal shift with single lobe atelectasis in this series of cases and it should be pointed out that this displacement was slight and was demonstrable only after the lobe had become reaerated. Bronchography revealed residual bronchiectasis in the affected pulmonary area. The poorly contrasted bronchiectatic shadows lay directly over the heart shadow. There is no clinical evidence of infection in this bronchiectasis.

Case 5: J. C., a white male, present age ten years. Upon admission to the hospital there was clinical and radiographic evidence of atelectasis of the right lower and middle lobes. Bronchoscopy revealed occlusion of the right main bronchus above the orifice

to the middle lobe bronchus. Purulent material aspirated from beyond the obstruction revealed acid-fast bacilli. Six months after admission there was clinical and X-ray evidence of some reduction in the degree of obstruction although lateral radiograms revealed that the middle lobe remained atelectatic. Further bronchoscopic studies were not allowed by the parents of this child and, because they decided to remove him from the hospital, bronchographic studies were made although it would have been preferable to wait for more marked clearing of the atelectatic areas for technical reasons if for no other. These bronchograms revealed a partial occlusion of the right main bronchus at and above the level of the middle lobe bronchus and no iodized oil entered the atelectatic middle lobe. The radiopaque medium could be seen to trickle slowly through this incomplete obstruction under fluoroscopic observation. The bronchograms revealed bronchiectasis in the right lower lobe. This patient was not ill during his hospital stay and there was no evidence of the onset of infection in the bronchiectatic areas.

Case 6: W. M., a Negro male, present age two and one-half years. Upon admission to the hospital there were clinical and X-ray evidences of an atelectasis of the left lower lobe. Four months later the entire left lung had become atelectatic but there was no mediastinal shift at that time. One year after admission there was some reduction in the completeness of bronchial obstruction, although mediastinal shift to the left had taken place (figure 4A) and this alteration persists. Subsequent bronchography (figure 4B) revealed bronchiectatic changes throughout the left lung and bronchoscopy showed that there was a partial stenosis in the left main bronchus which reduced the diameter of the bronchus by approximately one-third. This patient was critically ill during the period of maximum bronchial obstruction. Wheezes, rhonchi and musical râles were prominent. At present there is no evidence that infection is present in the bronchiectatic areas of the left lung.

Case 7: F. R., a Negro male, present age six years. Upon admission to the hospital there were clinical and roentgenographic evidences of atelectasis of the entire left lung with mediastinal displacement to the left side. Wheezing, rhonchi, and musical râles were marked and the patient was desperately ill for three months. Bronchoscopy revealed occlusion of the left main bronchus, although it was possible to pass a specimen collector beyond this obstruction for the purpose of aspirating purulent secretions. Eight months after admission the obstruction was no longer present and the left lung became reaerated and a definite shift of the mediastinum persisted. Later, bronchograms of both the right and left bronchial tree were made. Comparative studies revealed moderate but definite and wide-spread dilatation of the bronchial lumina on the left side. At this time there was no clinical evidence of appreciable infection in the left lung.

Case 8: E. M. T., a Negro female, present age three years. Five months after admission to the hospital there were clinical and roentgenographic (figure 5A) evidences of

---

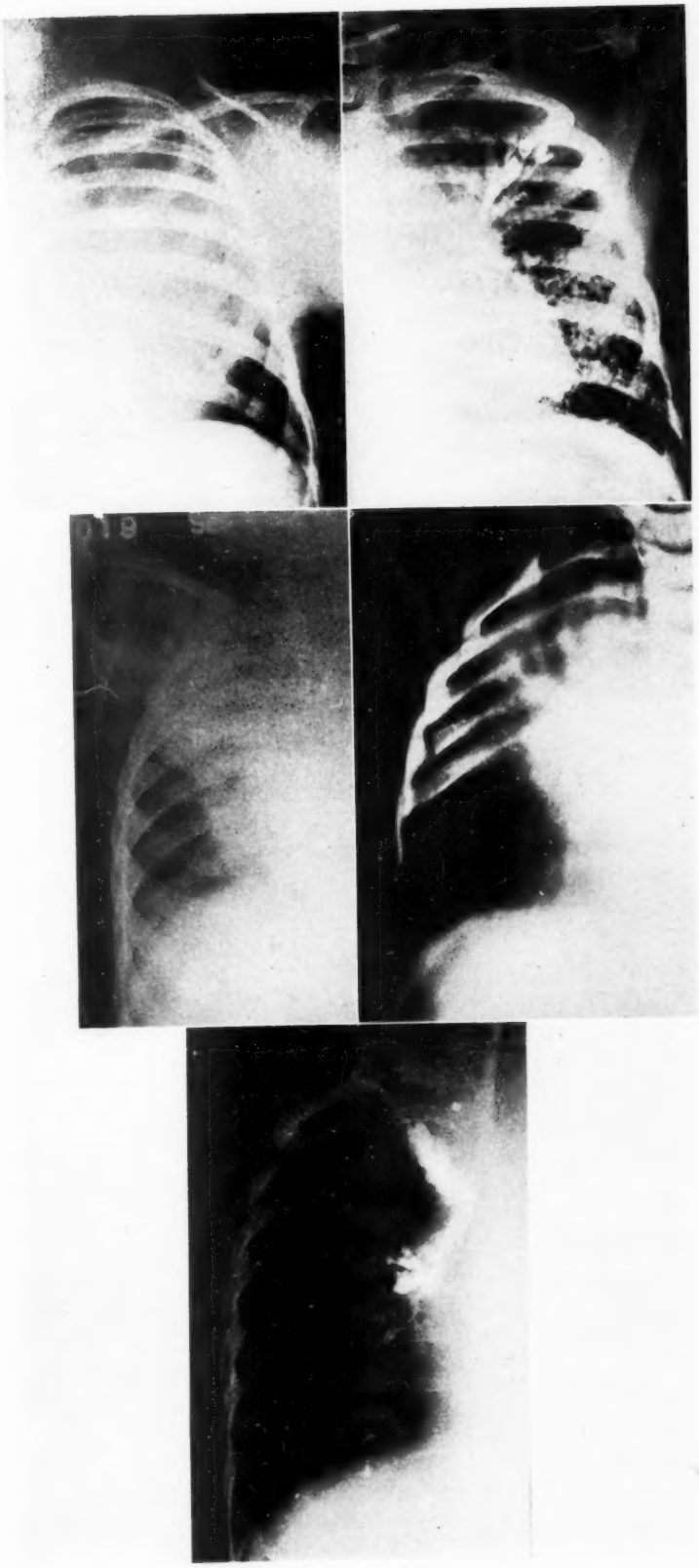
FIG. 1A. Upper left. Atelectasis of left upper lobe.

FIG. 1B. Upper right. Bronchiectasis as a sequela of the atelectasis in left upper lobe.

FIG. 2A. Center left. Atelectasis of right upper lobe.

FIG. 2B. Center right. Laminogram which reveals the bronchiectatic structure of lobe.

FIG. 2C. Lower. Bronchogram which reveals bronchiectasis and retraction of the right upper lobe. There is also bronchiectasis in the apex of the right lower lobe.



FIGS. 1A–2C

atelectasis of the right middle lobe. The mediastinal and hilar lymph nodes were unusually prominent in the chest roentgenogram. This child was not affected clinically by the transitory atelectasis and four months later there was marked clearing on roentgenographic study of the chest, and the physical examination confirmed this observation. Ten months after the atelectasis was detected, bronchographic studies were prepared. These special examinations are often difficult to achieve satisfactorily in young children and in this instance a poor filling of the right middle lobe resulted (figure 5B). However, no evidence of bronchiectasis was seen. This child presents a transitory atelectasis without secondary bronchiectasis.

Case 9: J. W., a Negro male, present age three and one-half years. This patient was admitted to the hospital with tuberculous lymphadenitis which was most marked in the cervical groups. Six months after entry an atelectasis of the left upper lobe was indicated by clinical and roentgenographic examinations. There were no symptoms save moderate wheezing, and four months later the obstruction had become less complete with reaeration of the affected pulmonary segment. One year later bronchograms were prepared which revealed no bronchiectasis. This patient is the second instance of transitory atelectasis without bronchiectasis.

Case 10: G. D., a Negro male, present age two years. This child presented clinical and roentgenographic evidences of atelectasis of the left lower lobe upon hospital entry. Within four months this atelectasis had disappeared. The child was not affected by the atelectasis as far as could be determined, although wheezing, rhonchi and musical râles could be heard. One year after the atelectasis had been detected, bronchograms were prepared which demonstrated no residual bronchiectasis. This is the third case in this series which presents a transitory atelectasis without bronchiectatic sequelae.

DISCUSSION

Among these 10 cases of atelectasis, occurring during the course of childhood pulmonary tuberculosis, there are 7 which have bronchiectatic changes which are undoubtedly secondary to the bronchial obstruction. An effort has been made to determine the reason why 3 patients do not show bronchiectatic sequelae. Similar atelectasis resulting from bronchial obstruction of varied but quite different circumstances has been recognized for many years and it is not surprising that such residual changes in the bronchial structure should be found in these cases.

The universal factors acting in any instance of bronchial occlusion to produce secondary bronchiectasis are the degree of obstruction, the duration of the occlusion of the bronchus and the presence and the severity of the infection set up in the pulmonary segments compromised by the bronchial closure. Except for the

---

FIG. 3A. Upper left. Atelectasis of the right upper lobe.

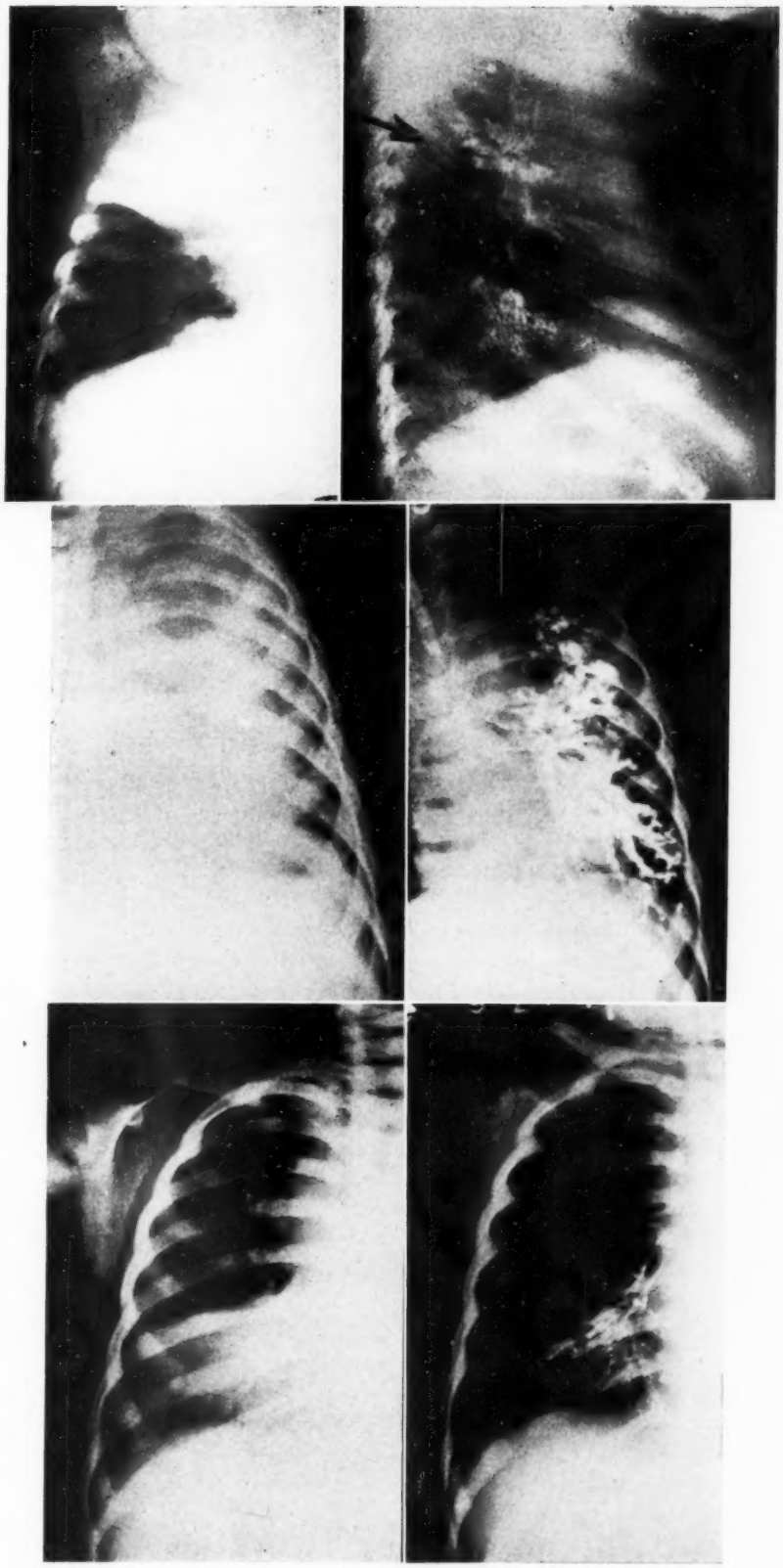
FIG. 3B. Upper right. Lateral view revealing upper lobe bronchiectasis.

FIG. 4A. Center left. Atelectasis of entire left lung with retraction of mediastinum.

FIG. 4B. Center right. Bronchogram which reveals bronchiectasis in the entire left lung.

FIG. 5A. Lower left. Atelectasis of right middle lobe.

FIG. 5B. Lower right. Bronchogram which reveals no bronchiectasis.



FIGS. 3A–5B

2 cases of atelectasis of an entire lung there has been little clinical evidence of infection in the atelectatic areas in this study. It has not been possible to determine with accuracy the completeness of the obstruction in these cases. The one factor upon which there has been a reasonably satisfactory control is the duration of bronchial obstruction and consequent pulmonary atelectasis. In general those instances in which the time interval has been less than six months have escaped secondary bronchiectasis.

The absence of residual bronchial stenosis of any appreciable degree lends support to the contention that the obstruction of the bronchus is the result of extrinsic compression rather than of intrinsic bronchial disease.

It is worth noting that the expected shift of the mediastinum and its contents has been demonstrable only when an entire lung became atelectatic. Obstruction of a primary bronchus with lobar collapse has not brought about this change, an observation noted by Terplan (2).

The cases of lobar atelectasis were not particularly ill during the course of the bronchial occlusion. This indicates that there has been relatively little infection in the affected areas of the lung. Such observations suggest that these patients might easily pass without detection under less favorable circumstances for diagnosis. The 2 instances of major bronchus occlusion with atelectasis of the entire lung were very ill at the height of the process.

Wheezing, rhonchi and musical râles were present in several of these cases and were suggestive of an asthmatic syndrome. This is a possible pitfall in diagnosis.

The question arises whether cases of this sort contribute appreciably to the incidence of infected bronchiectasis. This series of cases presents a much larger percentage of upper lobe bronchiectasis than is seen in any general study of the problem of infected bronchiectasis and a natural conclusion is that this syndrome plays little part in the whole picture. The fact that not one of these children provides symptoms of infection, as yet, is of some confirmatory value in assessing the importance of the syndrome. Further observation of these young patients with this and other features in mind would be valuable.

Among the 8 cases of lobar atelectasis, 7 ultimately became aerated while only one remained collapsed and in this instance the bronchus has been proven to be open. The 2 patients with atelectasis of an entire lung present somewhat more marked residua. There has been an incomplete reversal of the mediastinal shift and there are rather marked secondary changes producing a diminished radiotransparency.

Nine of these 10 cases occurred in Negro children and the census of the children's wards on which they were found is over 80 per cent Negro patients.

CONCLUSIONS

1. Ten cases of lobar or pulmonary atelectasis during the course of childhood tuberculosis have been presented.

2. Evidence that the bronchial occlusion is the result of external pressure by aseating peribronchial lymph nodes has been offered.

3. Secondary bronchiectasis has been shown to be a result of this bronchial obstruction in 7 of the 10 cases.

4. There is evidence that changes of such origin do not play an appreciable rôle in the aetiology of infected bronchiectasis.

5. These cases add to the accumulating evidence that the so-called epituberculous pneumonia is in reality atelectasis resulting from occlusion of a bronchus.

6. The prognosis of this syndrome appears to be favorable.

CONCLUSIONES

1. Preséntanse 10 casos de atelectasia lobular o pulmonar durante la evolución de la tuberculosis infantil.

2. Ofrécense pruebas de que la oclusión bronquial es el efecto de la presión externa por casear los ganglios linfáticos peribronquiales.

3. Demuéstrase que la bronquiectasia secundaria es resultado de dicha obstrucción bronquial en 7 de los 10 casos.

4. Hay pruebas de que las alteraciones que reconocen ese origen no desempeñan papel apreciable en la etiología de una bronquiectasia infectada.

5. Estos casos agregan nuevos datos a los y acumulados en el sentido de que la llamada neumonía epituberculosa es en realidad una atelectasia debida a la oclusión de un bronquio.

6. El pronóstico de este síndrome parece ser favorable.

REFERENCES

(1) Roessle, R.: Virchows Arch., 1936, *296*, 1.
(2) Terplan, K.: Anatomical studies on human tuberculosis, Supplement to Am. Rev. Tuberc., August, 1940.
(3) Wallgreen: Acta. radiol., 1926, *7*, 229.

TUBERCULIN SENSITIVITY IN CHILDREN WITH BONE TUBERCULOSIS[1]

PHILIP J. HOWARD, JOSEPH A. JOHNSTON AND C. LESLIE MITCHELL

QUANTITATIVE TUBERCULIN TESTING IN BONE TUBERCULOSIS

The relation of allergy to bone tuberculosis is complex because bone infection is a complication rarely found alone. It usually has been preceded by primary lung or hilar lymph node infection, a process itself accompanied by a rise in allergy and a later fall in allergy with calcification, over a two-year period. Bone lesions have a tendency to be multiple because they are metastatic. Production of tuberculin is probably proportional to the size and number of the lesions. Children with bone lesions, since they have been through a stage of blood-borne infection, are likely to have lymph node, skin and general infection. Our finding of some extremely high thresholds of reaction in bone infection is not different from that of other authors who have investigated this point (1, 2), but these high levels are, in our opinion, attained only after the full development of the tuberculous bone lesion. Lower levels are characteristic of the disease in its beginning and do not exclude the condition, as has been suggested. We have been fortunate in seeing the curve of allergy in at least 4 patients who ran a long typical course of bone tuberculosis. These children had low reaction at first, ran through later high reactions and finally subsided to a low level. Many children were seen who had a medium or high level of sensitivity to tuberculin when first tested and later changed to a low degree of sensitivity. No particular level of sensitivity was found at first, except that the test was positive in the case of early vague joint symptoms, before X-ray examination showed bone destruction. Those children whose allergy subsided to a permanent low level were more likely to stay healed than those whose sensitivity level remained high.

Study of tuberculin test was advanced by Baldwin (3) who found that allergy often was so exaggerated that harm resulted from toxaemia and ulceration. Miller (4) expressed the conception that tuberculin allergy is a changing phenomenon to be considered in relation to the amount of infection and gave importance not to the momentary level but to the relative changes in either direction. Rich (5) found that allergy indicated primarily hypersensitive tissue that is more readily killed by tuberculoprotein. Rich and McCordock (6) studied factors of importance in pathogenesis of human tuberculosis and expressed the belief that, in allergy with overwhelming infection, most of the antibody was combined with large amounts of antigen released into the blood stream. It was their feeling that allergy and immunity were coincidental in their development but independent and unrelated phenomena. The accepted fact that at times hypersensitivity is a definitely harmful factor (5) brings up the question whether sensitization can be induced by intracutaneous injection, which is answered negatively

[1] From the Department of Pediatrics and the Division of Orthopedic Surgery, Henry Ford Hospital, Detroit, Michigan.

by Nelson, Mitchell and Brown (7) and by Krause (8), and Zinsser (9), but Appel *et al.* (10), however, have occasionally seen sensitization induced this way.

Daily variations in the tuberculin test are described by Howe (11, 12) using a constant dose of tuberculin and measuring the diameter of the area of reaction. He showed also a decrease of the reaction with vasoconstriction of the capillaries of the skin. In 1930, at the start of the present study, this method of measuring the diameter of reaction to a constant dose of OT was tried by us on children and discarded as not accurate enough to follow the wide variations in reactivity. The method of dilution of OT, though cumbersome, has proved more precise and easily interpreted. Landorf (13), using single tests only, reported variations in sensitivity, the highest sensitivity in fresh primary lesions, the lowest in miliary and meningitic infection. Extreme examples of loss of sensitivity, in one case to 100 mg. OT, are reported by Lindgren (14) and Roberts (15). To understand these cases, a knowledge of the course of sensitivity over a long period of years in even a few children is valuable. A tuberculous patient who does not react to 100 mg. of OT is in an extreme phase of anergy.

The experimental work of Willis (16, 17) showed that some animals retained a high immunity in the presence of gradually declining cutaneous allergy and, in other experiments, some of the desensitized animals succumbed to the most gross type of experimental tuberculous pneumonia. Follis (18) performed experiments in which the animals were desensitized to 2 cc. OT daily, given intravenously, and found less necrosis and caseation in these desensitized animals than in the controls, although they still succumbed to the disease. A few carefully selected adult patients were cautiously desensitized by Willis (19) and the results were somewhat beneficial. He (20) stated it was his opinion that desensitization in animals is associated with apparent immunity for a few weeks, but that prolonged desensitization eventually undermines the resistance. The violent reactions, occasionally seen to tuberculin, make caution desirable in the undertaking of even the simplest course of desensitization injections (21, 22).

Dickey (23) noted an increase in the size of the skin reaction in direct relation to the age of the child, which is to be understood as a summation of exposure and disease. He found high sensitivity with phlyctenules, lymph node and bone infections, drawing his conclusions from a single test and measurements of the diameter of the reaction. Lincoln (24) stated she found no correlation between size of the reaction and the location, size or activity of the lesion nor the prognosis. She stated also that it was undesirable to repeat the test if once found positive. If no tests are repeated it practically means the end of investigation of the field of skin allergy to tuberculin in children, a field which we believe may still furnish useful information. Schwartz and Heise (25) and Hayes (26), using a technique to which ours is very similar, investigated many examples of adult tuberculosis without demonstrating any correlation between skin reactivity and height of immunity. Atsatt's (1) comprehensive and detailed paper showed a quantitative difference in skin reactivity to dilutions of OT in bone tuberculosis. The weakest dilution he used gave a skin test dose of 0.01 mg. OT, quite a strong test in the light of further work. His conclusion was justified that where allergy

TABLE 1

Course of allergy to OT in bone tuberculosis

CASE NUMBER		DISTRIBUTION OF DISEASE	AGE OF BONE INFECTION AT FIRST TEST	LEVEL OT SENSITIVITY IN MG.						
				First	Interval in years	Highest dilution	Interval in years	Final	Healing*	
1	C. H.	Lungs, primary Hip	At start	0.1	1	0.000,001	6	0.1	Slow	Cases 1 to 4 show course of allergy from start of infection to healing. Best examples of rise and fall of sensitivity.
2	R. K.	Lungs, primary Hip	At start	0.01	$\frac{10}{12}$	0.000,000,01	6	0.001	Medium	
3	R. S.	Lungs, primary Spine Tonsils, knee	At start	0.01	$1\frac{5}{12}$	0.000,001	$1\frac{7}{12}$	0.01	Slow	
4	E. W.	Lungs, primary Spine, phlyctenule Pleurisy	At start	0.01	$\frac{4}{12}$	0.000,000,01	$2\frac{4}{12}$	0.001	Medium	
5	G. L.	Lungs, primary Spine	5 to 10 months	0.001	$\frac{10}{12}$	0.000,1	3	0.01	Slow	Cases 5 to 11 show partial course of allergy demonstrating the rise and fall, but not complete.
6	G. M.	Lungs, primary Elbow	5 to 10 months	0.000,1	$\frac{9}{12}$	0.000,001	$\frac{10}{12}$	0.000,01	Rapid	
7	S. O.	Lungs, primary Hip Phlyctenule abdominal lymph node	5 to 10 months	0.000,001	$1\frac{5}{12}$	0.000,000,000,01	6	0.001	Slow	
8	J. S.	Lungs, primary Malar bone	5 to 10 months	0.01	$\frac{4}{12}$	0.001	$\frac{6}{12}$	0.01	Rapid	
9	J. W.	Lungs, primary Carpal bones Tarsal bones	5 to 10 months	0.1	1	0.000,000,01	2	0.001	Medium	

10	J. M.	Lungs, primary Hip Elbow, Knee	5 to 10 months	0.001	2	0.000,000,01	$\frac{7}{12}$	0.000,01	Medium	
11	J. N.	Lungs, primary Hip	24 months	0.000,1	$\frac{4}{12}$	0.000,001	6	0.001	Slow	
12	J. A.	Lungs, primary Hip, cervical Lymph nodes	4 years	0.000,01	2	0.000,01	6	0.01	Slow	Cases 12 to 14 are late in course of bone disease showing only fall in allergy.
13	S. B.	Lungs, primary Hip Lungs	5 years	0.000,1	1	0.000,1	$1\frac{5}{12}$	0.001	Slow	
14	J. P.	Lungs, primary Pleurisy Spine	1 year	0.000,1	$\frac{5}{12}$	0.000,1	$\frac{4}{12}$	0.001	Rapid	
15	D. D.	Lungs, primary Face, hand, elbow Mesenteric lymph nodes	16 months	0.000,001	$1\frac{6}{12}$	0.000,000,1	$\frac{6}{12}$	0.000,001	Slow	Cases 15 to 19 show high plateau of extreme sensitivity and poor progress.
16	E. G.	Lungs, primary Hip	12 months	0.000,001	$1\frac{5}{12}$	0.000,000,1	2	0.000,001	Slow	
17	J. H.	Lungs, primary Hip	6 years	0.000,1	$1\frac{6}{12}$	0.000,1	$1\frac{6}{12}$	0.000,1	Slow	
18	H. B.	Lungs, primary Spine	3 years	0.000,000,01	1	0.000,000,01	1	0.000,000,01	Slow	
19	R. J.	Lungs, primary Spine Sacroiliac Kidney	At start	0.001	$1\frac{6}{12}$	0.000,001	6	0.000,001	Fatal spread	

* Slow—over five years.
Medium—two years to five years.
Rapid—under two years.

falls below the threshold of 0.01 mg. active tuberculosis may be fairly eliminated. We have a patient whose first threshold was 0.1 mg. and whose final threshold seven years later was 0.1 mg., but such patients are very rare. It is common to get a severe reaction in a patient with bone infection by applying such a strong test as 0.01 mg. OT. Blair and Galland (2) confirmed Atsatt's finding of high levels of allergy in bone tuberculosis, but the patients in both these studies were tested when their disease was fully developed. Several excellent studies of the quantitative allergy curve in primary tuberculosis have appeared showing a wide range of opinion. Appel (10) reported a group of healing childhood lesions in which the OT sensitivity over a period of nine months' observation increased in 9, decreased in 4 and remained constant in 8. Von Groer (27) attempts to select a group of healing childhood infections in which "the diameters of the skin reactions do not decrease in the expected degree," while we are satisfied to ascertain, if possible, whether the reaction increases, decreases or remains constant. The report by With (28) agrees that high sensitivity is present in active primary infection and a lower degree in healed primary infection. These studies are all pertinent, as bone tuberculosis in most instances cannot be separated from the primary infection, and it is a question of deciding where, in the course of the former, the latter is superimposed.

Our material consists of 19 patients with bone tuberculosis in whom we have followed the course of allergy as constantly as possible between 1930 and 1940. Dilutions of OT were prepared and tests carried out with enough dilutions to get an end point or threshold above which the patient did not react. One lot of OT, prepared at Saranac Lake, was used and the dilution carried out as previously described (29). Only specimen curves can be briefly shown, as many of these children had 20 threshold determinations each requiring 3 to 6 skin tests. The type of bone disease and the complicating forms of tuberculosis are shown in table 1. The length of time bone infection was present before the OT sensitivity measurements were started is tabulated. The first level, the highest and the final level of sensitivity with intervals in years are listed. Lastly, the total time in years to obtain bone healing is shown for comparison with the allergy curve. It is evident that, to show the full course of the allergy curve, observation must be started at the onset of bone infection.

Individual case summaries follow:

CASE REPORTS

Four cases followed through entire course, showing the increase and decrease of allergy:

Case 1. C. H.: A two year old white boy was admitted within two weeks of his first symptom, inability to walk. His hip was in fixation for five years. His OT sensitivity was low at first, climbed and receded over seven years. There was an active infection of the lungs and tonsils. His ability to heal was poor since he was under observation for nine years. Detailed curve of sensitivity is shown in figure 1.

Case 2. R. K.: A two year old white girl was admitted at the first complaint of limp. A clinical impression of a tuberculous hip could not be confirmed by X-ray studies until four months later. She progressed through a typical course of primary active pulmonary infection and hip involvement. Her OT sensitivity increased for ten months and, then, with healing, finally subsided over a period of six years. A detailed curve of her sensitivity is shown in figure 2.

Case 3. R. S.: A three year old white girl was admitted for primary pulmonary infection. She subsequently developed tuberculosis of the tonsils and spine and later

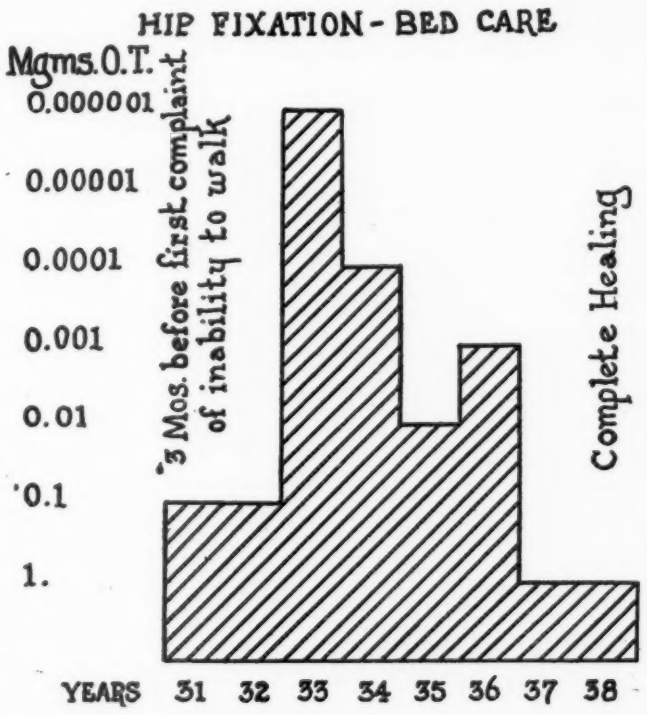


FIG. 1. OT sensitivity curve of case 1, Charles H., during course of tuberculous hip, from start to final healing.

of a knee. She was under fixation treatment for seven years and showed poor ability to heal. Her OT sensitivity (figure 3) was low at first, rising high and falling again with healing.

Case 4. E. W.: A two year old colored girl was admitted for primary pulmonary infection and later had pleurisy and involvement of the spine. Her bone involvement developed after she had had tuberculosis for two years. She showed good ability to heal the bone lesion, but her tuberculosis spread and she was still under treatment after nine years. Her OT sensitivity record is shown in figure 4.

Seven cases showing rise and subsequent fall in allergy, but not followed during entire course:

Case 5. G. L.: A two and one-half year old white boy was admitted for infection of an elbow and the spine. His kyphos was marked and produced a paraplegia. His OT sensitivity was low at the start, increased slightly for one year and then receded. He showed at first examination a healed primary pulmonary lesion.

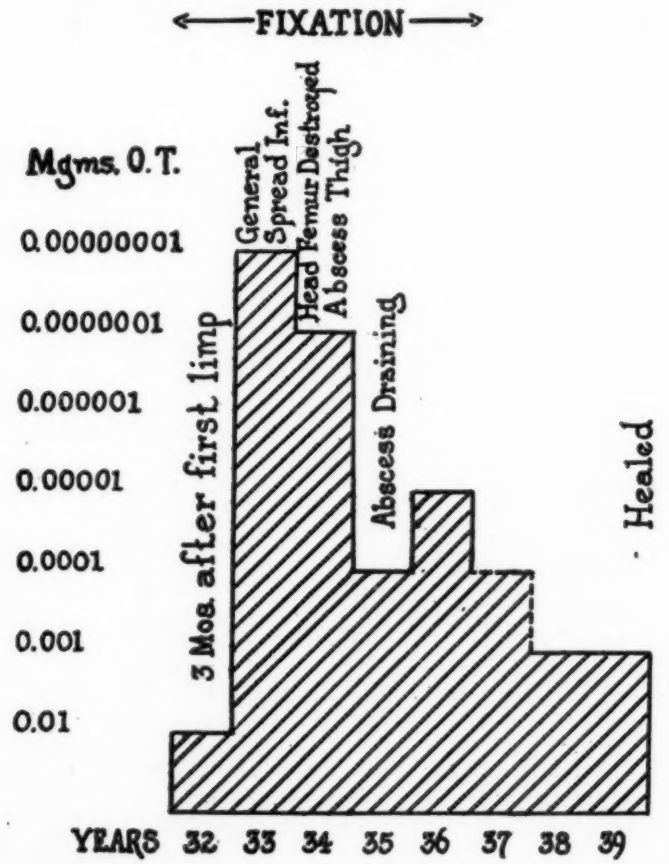


FIG. 2. OT sensitivity curve of case 2, Rose K., during course of tuberculous hip, from start to final healing.

Case 6. G. M.: A two year old Syrian boy was admitted for failure of his elbow to heal, six months after a fall which had injured his elbow. Examination showed active primary infection of the lungs and a tuberculous elbow. No other involvement appeared and he healed completely in two years. His OT sensitivity was medium at first, rose to high levels and subsided somewhat. He is an example of excellent ability to heal.

Case 7. S. O.: A two and one-half year old white boy, exposed to an open case since birth, showed an active primary tuberculosis of the lung and a hip infection. Five

months later he showed a phlyctenule. Over a period of five years he healed completely. His OT sensitivity was high when first tested, within two years of the onset of hip infection, and it remained the highest recorded in our experience for approximately eighteen months with reactions to a dilution of 10^{-11} of OT. This subsided to a low level in eight years.

Case 8. J. S.: A white boy, three years old, fell, injuring his face six months before admission. He was shown to have a primary lesion of the lungs and an infection of the malar bone. He healed quickly in one year. His OT sensitivity remained low.

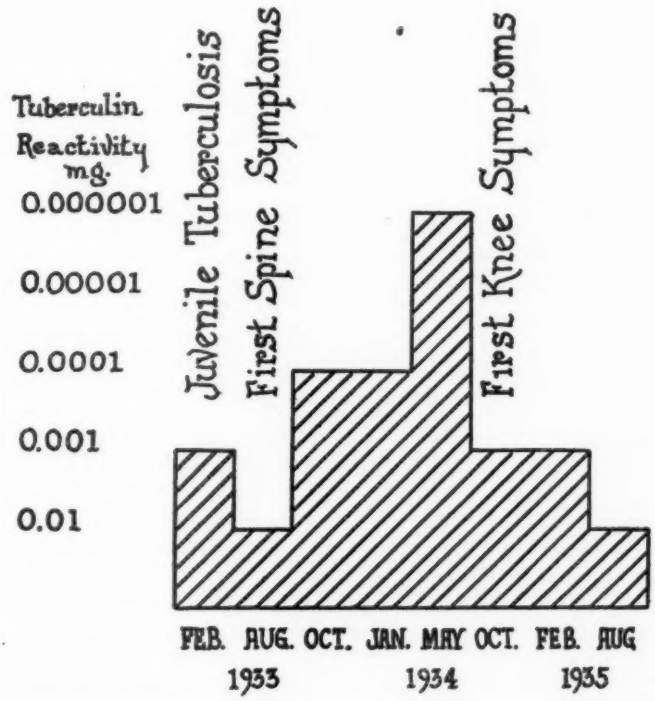


FIG. 3. OT sensitivity curve of case 3, Rita S., during course of tuberculous spine, complicated by tuberculous tonsillitis, and tuberculous knee infection.

Case 9. J. W.: A four year old colored boy was admitted with tuberculous carpal and metatarsal bones and later showed generalized haematogenous pulmonary tuberculosis and dacryocystitis, cervical adenitis and phlyctenule. His OT sensitivity was low at first and, with progression, it became high, finally, with healing, falling to a low level in three years. A series of 24 subcutaneous injections of tuberculin to desensitize him as treatment for severe phlyctenules did not hasten or retard the healing of bones. During this treatment his threshold to OT fell from 0.000,001 mg. to 0.001 mg.

Case 10. J. M.: A six year old colored boy was admitted for primary pulmonary infection, cervical adenitis and tuberculous hip which started with a fall three years previously. He developed later an elbow and knee infection. His OT sensitivity was low at first,

but remained high for nearly three years during which time his lesions were advancing. His joints all finally healed in ten years.

Case 11. J. N. A five year old white boy was admitted for a tuberculous hip of two years' duration which immediately followed a fall. He showed a healed primary pulmonary infection. His hip infection was active for seven years but finally healed. His OT sensitivity was medium when first tested, rose to high level and, with healing, receded to low levels.

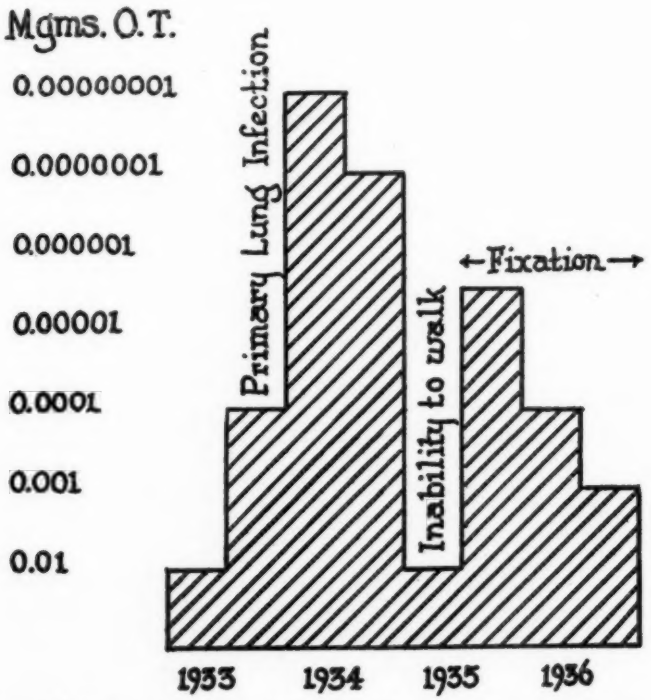


FIG. 4. OT sensitivity curve of case 4, Earlene W., during course of primary infection followed by tuberculous spine. Secondary pulmonary tuberculosis followed in 1937.

Three cases late in course of disease, showing only fall in allergy:

Case 12. J. A.: An eight year old Mexican boy was under treatment four years for a primary lesion of the lungs, cervical lymph nodes and hip. The process in the hip and lung was practically healed when he was admitted in 1931. No more fixation was needed. Sensitivity to OT was high from 1931 to 1935, during which time he had a large weeping ulcerative tuberculosis of the skin. In 1941 his sensitivity was low and his skin lesions healed.

Case 13. S. B.: A thirteen year old white girl was under treatment for five years for a tuberculous hip and was admitted with draining sinuses. During her several years with us her sensitivity was medium and low, her ability to heal poor.

Case 14. J. P.: A white boy, ten years old, had a primary pulmonary tuberculosis with pleurisy for two years prior to admission. Spine infection had been present for six months. He showed excellent ability to heal and was only in fixation for one year. His OT sensitivity was medium, falling under observation.

Five cases showing a sustained high plateau of sensitivity from two to seven years:

Case 15. D. D.: A nine year old colored boy at admission had generalized tuberculosis, affecting his face, hands, right elbow, mesenteric lymph nodes and spleen. On admission the process was sixteen months old. His sensitivity was high and he showed only a slight healing in two years, so that at the end of observation his disease was still active. Healing continued and was satisfactory in six years. No late OT tests could be obtained.

Case 16. E. G.: A twelve year old white boy came twelve months after the first symptom of a painful hip. He already had calcified hilar nodes. Fixation of the hip was carried out for five years. Sinuses were still draining eight years later. His sensitivity was high for four years and he showed poor ability to heal.

Case 17. J. H.: An eleven year old white girl was treated for six years for tuberculous spine and, on admission, the process was advanced with marked kyphos and a healed primary focus in the lungs. Her sensitivity was medium and she did not improve in four years.

Case 18. H. B.: A six year old white boy had his first symptom of pain in the back three years before admission. He was given fixation treatment of the spine. His sensitivity was high during his entire stay of two years. His ability to heal was poor and he had an active infection at the end of observation.

Case 19. R. J.: A nine year old white girl was admitted with a haematogenous generalized pulmonary infection and there followed, at intervals during the next three years, multiple infections of the spine, the sacroiliac joint, the cervical lymph nodes and a psoas abscess. Over a period of ten years she showed poor ability to heal. Her OT sensitivity was high for eight years. After ten years of care she developed tuberculosis of both kidneys and lost ground rapidly.

COMMENTS

The 19 patients selected for presentation all had active tuberculous osteomyelitis of one or more regions, and all showed evidence of primary pulmonary infection, active or healed. Nine of them showed multiple bone involvement or other tuberculous complications.

The first 4 children, cases 1 to 4, were infants aged two years, followed through the major portion of their disease, and all were under observation from the start of the bone infection. This gave an opportunity to follow the course of their sensitivity to OT. The first levels were 0.1 mg. in one and 0.01 mg. in the other 3. To appreciate what low levels these were, a glance at the height to which they went is needed, the level being 0.000,001 mg. in 2 and 0.000,000,01 mg. in two. These extreme levels, maintained over a period of three to seven years,

subsided to levels of 0.001 mg. or less with healing. These 4 cases represent our closest approach to the total curve of allergy in bone tuberculosis, because they were infants on admission, because they appeared for treatment at the start of their bone infection, because we had contact with them over an extended period of years and because they had a minimum of complicating foci.

The second 7 cases are of the same general type, but were first observed five to ten months after the start of bone infection. The first observed levels of allergy were more scattered, but the rise and later fall with healing were demonstrated. The height of the first observation in many cases, for example case 7 where it was 0.000,001 mg. OT, may have been dependent not on the bone infection but on the primary pulmonary infection or other complications. One might conclude from these two groups that the onset and activity of complicating forms of tuberculosis tend to cause an increase in allergy which later falls with healing.

The third group, cases 12, 13 and 14, comprises children who appeared for care late in the course of their disease. They had been subject to bone infection for four years, five years and one year. Their sensitivity had already passed the crest and was subsiding. Case 14 had been showing Pott's disease only for one year when he came for care, but he was presumably already "late" in his disease because with falling allergy he healed the process in one more year. These 3 patients fit the same pattern of allergy curve as the preceding groups but, because the observations are late, the sensitivity is falling.

The last group of 5 shows an allergy curve which stayed on a high plateau of sensitivity for from three to six years. These patients showed extremely poor ability to heal and all had active lesions at the end of our period of observation. Case 19 was under our care at the start of her bone infection and her allergy curve showed a typical rise to high sensitivity. Then her level of sensitivity stayed high for six years, a period during which she underwent one tuberculous spread after another, until a fatal miliary spread and involvement of both kidneys developed.

The exact amount of OT causing the first observed tuberculin reaction is quite variable. This depends on the amount of tuberculous infection in the whole body, the size and number of bone infections, the glandular, pulmonary or other complications. Two of our cases had a level of 0.1 mg., 4 of 0.01 mg., but the basic statement which can be made is that the test must be positive. One child, case 2, showed a positive test and local signs of spasm about the hip four months before any X-ray signs of destruction appeared. The extremes of sensitivity are found if the test is done at the proper phase of the disease and they are not serious or poor prognostic findings unless the extreme sensitivity fails to recede. It has seemed that failure of sensitivity to recede over a period of three years indicated a poor prognosis, active infection and spread of the disease. There is strongly suggested a duplication of the parabolic curve associated with healing which we (29) previously reported in connection with the first infection in contrast with the failure of sensitivity to decline when the lesion fails to heal. Figure 5 shows the composite allergy curves of cases 1 to 11 as contrasted with cases 15 to 19.

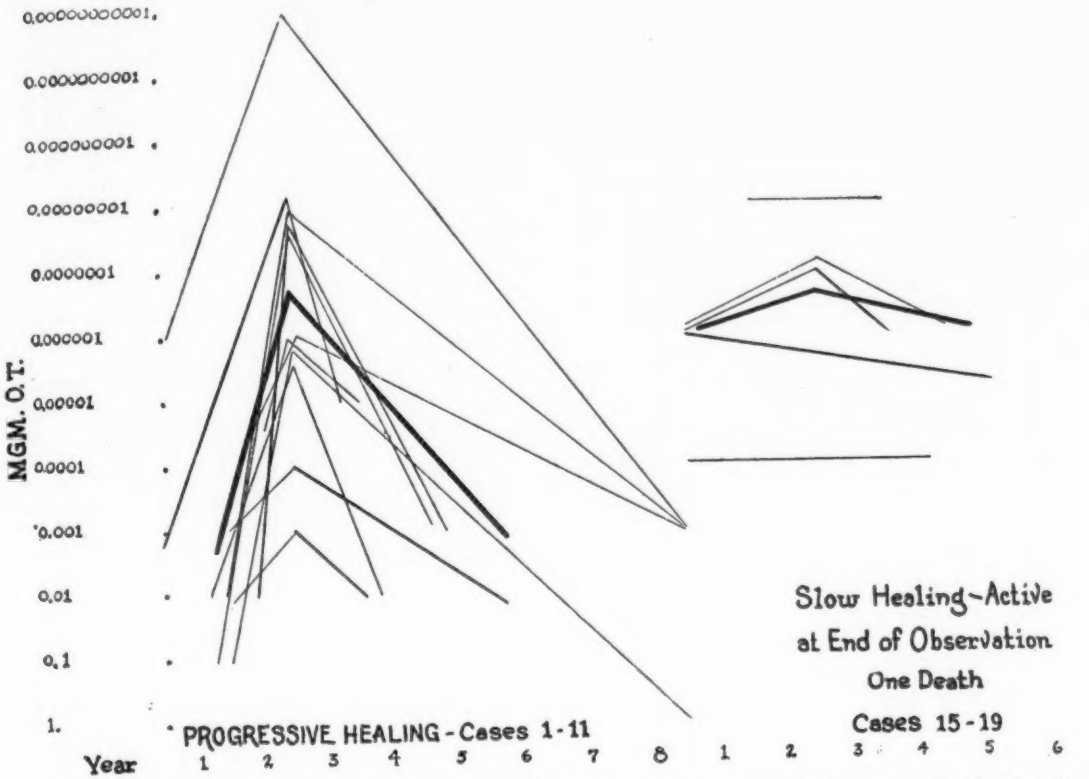


FIG. 5. A composite quantitative allergy curve to suggest the contrast between progressive healing and poor progress.

CONCLUSIONS

1. Sensitivity to tuberculin was measured by using dilutions of OT and determining thresholds of reaction in 19 patients with bone tuberculosis.

2. The initial threshold reactions in 4 children, cases 1 to 4, at the start of bone involvement were 0.1 to 0.01 mg. OT. These levels subsequently rose to 0.000,1 to 0.000,000,01 mg. and then receded again to levels of 0.01 and 0.001 mg. with the healing of the process.

3. A second group of 7 children followed the same rise and fall pattern of allergy but did not appear for treatment at the start of bone involvement.

4. A group of 5 children, cases 15 to 19, showed a high plateau of sensitivity for from three to six years, associated with poor ability to heal, and one death from constant spread of tuberculous infection.

5. All children showed a positive test at the start of bone infection, in one case four months before bone destruction could be seen on an X-ray film.

6. On the basis of this admittedly small series, it is concluded that a rise to high level of sensitivity with a subsequent fall is characteristic of the evolution of the healing process in bone tuberculosis, and that sustained high levels of allergy have characterized lesions which have shown a failure to heal.

CONCLUSIONES

1. En 19 casos de tuberculosis ósea justipreciόse la sensibilidad a la tuberculina empleando varias diluciones de TA y determinando los límites de la reacción.

2. Las reacciones límites iniciales en 4 niños (casos 1 a 4) fueron a 0.1 a 0.01 mg. de TA al iniciarse la invasión ósea. Esas cifras elevάronse después a 0.000,1 a 0.000,000,01 mg. y por fin retrocedieron de nuevo a 0.01 y 0.001 mg. al cicatrizar el proceso.

3. Otro grupo de 7 niños manifestó el mismo patrón de alza y baja de la alergia, pero no se presentaron para tratamiento al iniciarse la invasión ósea.

4. Un grupo de 5 niños (casos 15 a 19), reveló una altiplanicie de sensibilidad por espacio de tres a seis años, asociada con poca capacidad curativa, y una muerte debida a diseminación constante de la infección tuberculosa.

5. Todos los niños revelaron una prueba positiva al iniciarse la infección ósea, y en un caso cuatro meses antes de poder observarse destrucción ósea en la radiografía.

6. Tomando por base esta serie reconocidamente pequeña, dedúcese que una elevación acentuada de la sensibilidad, acompañada de una baja subsecuente, es característica de la evolución del proceso curativo en la tuberculosis ósea, y que las lesiones que revelan falta de cicatrización caracterízanse por tenores altos sostenidos de alergia.

REFERENCES

(1) Atsatt, R. F.: Studies with quantitative tuberculin reaction as an aid in bone and joint diagnosis, J. Bone & Joint Surg., 1927, *9*, 657.

(2) Blair, J. E., and Galland, W. I.: Differential quantitative tuberculin test, Am. Rev. Tuberc., 1931, *23*, 479.

(3) Baldwin, E. R.: Allergy and reinfection in tuberculosis, Bull. Johns Hopkins Hosp., 1913, *24*, 220.

(4) MILLER, J. A.: Some unsolved problems of tuberculosis, J. A. M. A., 1938, *111*, 111.
(5) RICH, A. R.: Observations on the relation of allergy to immunity, Bull. Johns Hopkins Hosp., 1930, *47*, 189.
(6) RICH, A. R., AND MCCORDOCK, H. A.: An enquiry concerning the rôle of allergy, immunity and other factors of importance in the pathogenesis of human tuberculosis, Ibid., 1929, *44*, 273.
(7) NELSON, W. E., MITCHELL, A. G., AND BROWN, E. W.: Possibility of sensitization to tuberculin, Am. Rev. Tuberc., 1938, *37*, 286.
(8) KRAUSE, A. K.: The prevention of tuberculosis based on the relation of childhood infection to tuberculosis in adult life, Am. Rev. Tuberc., 1922, *5*, 994.
KRAUSE, A. K., AND WILLIS, H. S.: The effect of frequently repeated reinfection on allergy and immunity to tuberculosis in guinea pigs, Tr. A. Am. Physicians, 1924, *39*, 86.
(9) ZINSSER, H.: Studies on tuberculin reaction and on specific hypersensitiveness in bacterial infection, J. Exper. Med., 1921, *34*, 495; The Shattuck Lecture, 1925.
(10) APPEL, J. M., DOUGLAS, B. H., JOCZ, T. R., AND WILLIS, H. S.: Relation between tuberculin allergy and clinical course, Am. Rev. Tuberc., 1937, *36*, 303.
(11) HOWE, J. S.: Daily variations in tuberculin reaction—Range of variation in tuberculous and control subjects, Ibid., 1938, *37*, 264.
(12) HOWE, J. S.: Daily variations in tuberculin reaction—Relation to the vasomotor pressure, Ibid., 1938, *37*, 273.
(13) LANDORF, N.: Tuberculin, Svenska läk.-tidning, 1937, *34*, 643.
Die Tuberkulinempfindlichkeit bei verschiedenen Formen von Kindertuberkulose, Acta. pediat., 1937, *20*, 1.
(14) LINDGREN, S.: Tuberculin anergy in a case of osteo-arthritic tuberculosis, Svenska läk.-tidning, 1937, *34*, 1379.
(15) ROBERTS, E. F.: Variations in tuberculin allergy, Yale J. Biol. & Med., 1930, *2*, 341.
(16) WILLIS, H. S.: The waning of cutaneous hypersensitiveness to tuberculin and the relation of tuberculoimmunity and tuberculoallergy, Am. Rev. Tuberc., 1928, *17*, 240.
(17) WOODRUFF, C. E., AND WILLIS, H. S.: Allergy and desensitization in experimental tuberculosis, J. Immunol., 1939, *37*, 549.
(18) FOLLIS, R. H., JR.: Effect of preventing the development of hypersensitivity in experimental tuberculosis, Bull. Johns Hopkins Hosp., 1938, *63*, 283.
(19) WILLIS, H. S., AND JOCZ, T. R.: Treatment of tuberculosis by tuberculin desensitization, Am. Rev. Tuberc., 1939, *39*, 318.
(20) WILLIS, H. S.: Story of tuberculin, Ibid., 1940, *41*, 573.
(21) BEHRENDT, H.: Undesirable tuberculin reactions, Acta. paediat., 1938, *23*, 129.
(22) WRIGHT, H. P., AND BACAL, H. L.: Allergic tuberculous purpura, Am. J. Dis. Child., 1937, *53*, 1276.
(23) DICKEY, L. B.: The size of the reacting area in intracutaneous tuberculin tests in relation to classification of disease and to other clinical factors, Ibid., 1929, *38*, 1155.
(24) LINCOLN, E. M., RAIA, A., AND GILBERT, L. A.: Tuberculin reactions in children, J. Pediat., 1938, *12*, 479.
(25) SCHWARTZ, W. S., AND HEISE, F. H.: Variations in tuberculin sensitiveness in tuberculosis patients, Am. Rev. Tuberc., 1931, *24*, 479.
(26) HAYES, M. G., PASTOR, J. R., GALTAN, L. R., CORY, R. A. S., AND LONG, E. R.: Tuberculin skin sensitivity in chronic tuberculosis in the course of hospital treatment, Am. J. M. Sc., 1937, *194*, 220.
(27) VON GRÖER, F.: New possibilities in a prognostic diagnosis in tuberculosis of children, J. Pediat., 1935, *6*, 297.
(28) WITH, T. K.: Tuberculosis in children with special reference to the clinical significance of graduated intracutaneous tuberculin reactions, Acta. paediat., 1937, *19*, 482.
(29) JOHNSTON, J. A., HOWARD, P. J., AND MARONEY, J.: Quantitative study of tuberculin reaction in childhood tuberculosis, Am. Rev. Tuberc., 1934, *29*, 652.

HASTINGS ON CATHETER DRAINAGE OF TUBERCULOUS CAVITIES[1]

JABEZ H. ELLIOTT

The wide-spread interest in our sanatoria in the Monaldi suction aspiration of tuberculous cavities seems sufficient reason to recall some early attempts at catheter drainage. Monaldi refers to the cases reported by Hastings in 1845. A copy of Hastings' work has come into my possession recently and as the work is not readily available in libraries it would seem desirable to make his contribution known.

John Hastings in *1843* published a work *Pulmonary Consumption Successfully Treated with Naphtha.* Our interest lies in the second edition which bears the above title to which has been added *And an Appendix Showing the Utility of Puncturing Tuberculous Cavities, as an Adjuvant in the Cure of Phthisis,* and was published in London by John Churchill in 1845.

In this appendix (page 225) he says that more than a century ago Dr. E. Barry (1, 2) of Dublin recommended puncturing tuberculous cavities as a means of curing phthisis. He published several cases in which his method had been employed with a successful result. Hastings thought the method was neglected partly owing to the difficulty the physicians then experienced (the stethoscope was not in use until 1820) in diagnosing the existence and precise situation of cavities. Without such knowledge the operation is fraught with danger and one fatal case is reported, the result being due to inability to locate the cavity. Hastings believed that with the discovery of auscultation and the application of percussion the method ought to have been revived.

Barry has observed that the irritation occasioned by the distention and contraction of the walls of cavities through the act of respiration was one of the chief obstructions to the healing process—the want of sufficient rest in the organ successively enlarged and contracted by respiration.

Hastings, then, includes 2 case reports by Sir Henry Marsh of Dublin, treated about 1830, but these were by open incision, not by catheter drainage. The one which recovered was probably an abscess or *empyema necessitatis.* From Hastings' résumé of the Barry cases most of them appeared also to be empyema and treated by open drainage. In his own cases Hastings based treatment on his belief that the persistence and augmentation of these cavities first caused by the ripening of tubercles was due to the distending and irritating effects of the air within the cavity. "Hence the object was to remove this, which appeared to me might be effectually done were a tube of sufficient calibre passed into the cavity, that would admit the escape of air as fast as it entered, so that, a state of repose being secured the walls of the cavity would be in a much more favourable condition for healing" (page 236).

The first case he reports (his case LIV) was treated by open incision into the

[1] From the Department of History of Medicine, University of Toronto, Toronto, Ontario, Canada.

cavity November 15, 1844. On the 17th the lint was removed from the wound and a piece of elastic gum tube inserted into the cavity. On the 23rd he noted that when the tube became displaced and touched the opposite side of the cavity a heavy sickening pain resulted, relieved by restoring the tube to its former situation. By November 28 the sputum had lost its purulent appearance.

The operating surgeon, Mr. Stokes, describes (page 249) his procedure in opening through the *pectoralis major* down to the third intercostal space below the cavity, and entering the cavity with a fine hydrocele trocar. He endeavoured to introduce a silver drainage tube but it did not answer the purpose well, and on the third day used a piece of elastic gum catheter, "which has been worn ever since, and found to answer the purpose better than any other kind of tube."

The walls of the cavern he found quite dense, almost cartilaginous. His description makes it quite clear that he was in a cavity, not simply in the pleura.

Working without anaesthesia the surgeon of the time wasted no time. In speaking of his second case and the method of incision used he says, "The simple proceeding adopted in the last case will, in the majority of instances, be found quite sufficient occupying as it does a few seconds only; it is, as far as the pain of an operation is concerned, not calculated to cause more suffering than the infliction of a wound necessary to evacuate the contents of a small abscess. After the incision is made, a piece of full sized elastic gum catheter is to be introduced along the wound into the cavern, and retained in its position by a piece of ligature tied around the end (which should project a quarter of an inch beyond the external wound), and the ligatures should be secured by strapping."

He fixed a warm sponge over the end of the tube to warm the entering air, and to absorb discharge, cautioning that it should be changed frequently.

He points out, on page 254, the importance of whether the *pleurae costalis* and *pulmonalis* adhere, which will be found to be the case in almost all cases in which the operation is applicable. The surgeon, he says, cannot divest his mind of the danger of creating a pneumothorax should there be no adhesions present, but quotes Louis "if there were no adhesions, rather would there be medium or large sized excavations."[2]

Hastings further writes, "Since the publication of I.G.'s case a similar operation has been performed by Mr. Thomas, a surgeon in Wales. When the report was published, a month after the operation, the patient had undergone great improvement."[3]

In his final paragraphs Hastings says: "The great majority of phthisical cases are, I am persuaded, wholly unfit for this mode of treatment, as the disease generally developes itself in both lungs to such an extent, that when a cavity exists in one, if there be none in the other, a crop of miliary granulations, or hardened tubercles, are met with, which so impair the function of respiration, as to form an insuperable barrier to the operation. But although this is generally true, so common is the disease that cases are occasionally met with, where

[2] Walshe's Translation, page 36.
[3] Hastings, page 258.

a cavity is formed in one lung, with very limited and recent disease in the other; and in rarer cases, one lung is perfectly healthy. Louis has recorded several examples of the latter, which are the cases that should be selected for puncture.

"The facts already accumulated, relative to this operation, are sufficiently numerous to show that life has not only been prolonged by its performance, but that recoveries have actually taken place, which entitles it to a full and impartial consideration by the profession. It must be borne in mind that the period when this valuable appendage to the treatment is admissable, the prospect of recovery through internal remedies is indeed very slight. I trust, by a careful selection of cases, in the course of a few years, that such an amount of success will have been realized as to enrol this part of the treatment amongst the most useful in the last stage of phthisis."

Doctor Hastings' cases are instructive. He knew nothing about blocked cavities but did believe in the distending effect of air within the cavity, the ill effect of retained secretions and in the need for rest of the cavity walls to ensure healing. He found the elastic gum catheter preferable to any other kind of tube. He did not use suction drainage. In this second edition of his book he records 2 cases treated by drainage.

Who was John Hastings? On the title page of this volume he appears as Senior Physician to the Blenheim Street Dispensary. From an obituary notice in *The Medical Times & Gazette* of January 2, 1875 we learn that he died two weeks previously in his seventieth year of heart disease. The writer speaks of him as a well known physician who began practice in the Vauxhall Road, but during his last thirty years practiced in Albemarle Street, Piccadilly, choosing for his specialty consumption and its treatment.

His book has the appearance of having been written for the public as well as for the profession. He would appear to have been one of those men who, with moderate ability and little acquirements, can achieve, by a persistent course of publishing works and advertising them, a certain amount of success, but which usually terminates in failure. He was considered a man of consummate tact, with a pleasing genial manner, severely and perhaps justly criticized by his fellow physicians because of his self-advertising and ill balanced deductions. Yet in all the relations of private life he was exemplary.

REFERENCES

(1) Barry, E.: A Treatise on Consumption of the Lungs, Dublin, 1726.
(2) Barry, E.: A Treatise on Three Different Digestions, London, 1763.

SURVIVAL OF TUBERCLE BACILLI IN BOOKS[1]

How Contaminated Books May Be Rendered Noninfectious

C. RICHARD SMITH

The following questions asked by our librarian, Mrs. Margaret Heiskell, provided the stimulus for this study: Are books and magazines that have been used by sputum-positive patients infectious? That is, is it safe for sputum-negative patients, student nurses and other members of the Sanatorium staff to read such books? Should positive patients be allowed to read and return books or magazines loaned by friends or outside libraries? If exposed books are infectious, what can be done to render them safe for use by nontuberculous persons?

We began with the assumption that persons with open tuberculosis do deposit living, virulent tubercle bacilli on the pages of the books or magazines they read. It remained to show whether such microörganisms are later available for infection, that is, whether they are recoverable alive and for how long a time.

Tubercle bacilli are known to live in the dark weeks, months or even years. Dried sputum was found by Twitchell (1) to be infectious for guinea pigs after seventy but not one hundred and ten days in the folds of cloth; after four to eighteen weeks on the surfaces of wooden tongue blades by Arms and Wade (2); and after three hundred and nine days in watch glasses kept in a dessicator, by Soparker (3). According to Potter (4) cultured avian strains may live as long as two years completely deprived of air and water. In this laboratory (5) suspensions of cultured human strains in water and sputum, smeared on glass cover slips in 0.05 cc. amounts, were kept in the dark. At unheated room temperature, in different tests, the bacilli were still alive after nine, fifty-five and one hundred three days; nonrecoverable after forty, seventy-five and one hundred fifty-eight days, respectively. They were recoverable for longer periods when the dose deposited was larger and they appeared to live longer in the winter than in the spring and summer. At refrigerator temperature they were still alive after six and one-half months, nonrecoverable after fourteen. In identical preparations exposed to unfiltered room-light, tubercle bacilli lived from four hours to five days, were nonviable at one to twelve days.

In 1916 Kenwood and Dove (6) carried out some experiments to determine the infectiousness of contaminated books. Sheets of paper were held one foot in front of sputum-positive tuberculous patients while coughing, then folded and stored under a bell jar. In over half the cases washings were infective for guinea pigs at two days but in none at thirty-one days. Papers smeared by thumbs wet in mouths of patients were infective in four out of five inoculations at two days; in one out of six at a month. Attempts to recover living tubercle bacilli from library books that had been used by consumptives were unsuccessful. The authors conclude that there is little risk of spreading tuberculosis by contaminated books; that any risk may be avoided by a "quarantine" period of one month.

Recently Jacobs and Petroff (7) inoculated scrapings from pages of books on which

[1] From the Barlow Sanatorium, Los Angeles, California.

bacillus-positive patients had intentionally coughed and which they had contaminated with thumbs wet in their mouths. All animals were negative. These authors suggest storage of exposed books for "several weeks."

PROCEDURE

Artificially or naturally positive sputum was smeared in 0.05 cc. amounts on one-inch squares cut in but not removed from the leaves of books, magazines or stacks of paper. The smears were made to cover two-thirds to three-fourths of the surfaces of the squares which were cut to include print where present. The books were immediately closed while the pages were still wet and stored in a dark cupboard in an unheated room. At intervals these paper squares were removed with sterile forceps and shaken by machine with a weak alkaline solution to recover the tubercle bacilli for culture and guinea pig inoculation.

The artificially positive sputums were obtained by thoroughly mixing suspensions of tubercle bacilli grown on culture media in known negative sputum. The preparation of suspensions as well as the methods of recovery, culture and animal inoculation have been previously described (5). All suspensions were prepared from a virulent human strain, designated as no. 88, isolated in this laboratory and subcultured four to eight weeks. The naturally positive sputa were made up of three to five strongly positive specimens mixed by fifteen minutes of mechanical shaking. Estimates of bacillary content were made by counting the number of acid-fast bacilli in a stained smear made from a measured amount of sputum. Counts on suspensions of strain 88 have shown an average of 205,000,000 stainable rods per mg. of moist culture. The material from each test was cultured on four tubes of Petragnani's medium.

There were variations in the procedure for experiment 1. The pages were smeared over an area two by three inches with cotton swabs dipped in a watery suspension of tubercle bacilli. Some of the leaves were exposed to unfiltered northern roomlight in a manner previously described (5). Entire leaves were removed for recovery and culture. Culture was made on only two tubes of medium after treatment with oxalic acid.

The United States Weather Bureau Station at Los Angeles from which meteorological data were obtained is within two miles of and at about the same altitude as the site of the tests. Averages of the mean monthly temperature and relative humidity (at 4:30 a.m.) were computed by simply adding the mean values for the calendar months during which a test was run and dividing by the number of months.

RESULTS

Experiment 1: A watery suspension containing 0.1 mg. moist culture (an estimated 20,500,000 tubercle bacilli per cc.) was used. This was smeared on the pages of a catalogue having thin, firm, nonglossy paper; and, for comparison, on those of a blank tablet with rather thick, opaque, dull white paper. Catalogue and tablet were kept in the dark while some leaves removed from the catalogue were exposed to unfiltered northern roomlight. Cultures were made immediately; at four and twenty-four hours; at four, fifteen and sixty-one days. Specimens from both catalogue and blank tablet kept in the dark were strongly positive through fifteen days but negative at sixty-one days. Those from the

leaves exposed to roomlight were strongly positive through twenty-four hours but negative at four days and thereafter.

These tests were run during April and May of 1937. The mean temperatures for these months were 62° and 64°F., respectively, so that the average for the period was 63°F. The mean relative humidity values were 73 per cent and 82 per cent, respectively, with an average of 77 per cent.

It should be mentioned that the tablet paper used here broke down into a pulp during the processing. This did not appear to interfere with recovery of the microörganisms.

Experiment 2: A naturally positive sputum, pooled from three fresh specimens, estimated to contain 11,500,000 tubercle bacilli per cc. or 575,000 per single dose, was smeared on squares cut in the pages of a catalogue similar to that used in experiment 1. Culture, only, was performed immediately and at five, nine and fourteen days. Both culture and animal inoculation were done at eighteen, twenty-three, thirty, thirty-seven and forty-six days. Culture was strongly to moderately positive through fourteen, but negative at eighteen days and thereafter. Animal inoculation was strongly positive at eighteen but negative at twenty-three days and thereafter. Thus the experimental viability of the microörganisms lay between eighteen and twenty-three days. Animal inoculation was somewhat more sensitive as a method of recovery than culture, since it extended the period of proven survival by four days.

These exposures were made during the month of September when the mean temperature was 72°F. and the mean relative humidity (at 4:30 a.m.) 79 per cent.

Experiment 3: An artificially positive sputum containing the very large quantity of 10 mg. tubercle bacilli per cc., that is, 0.5 mg. or an estimated 102,500,000 microörganisms per smear, was employed. The book was a novel having the usual dull, loose-textured paper. Culture was performed immediately; culture and animal inoculation at fourteen, nineteen, twenty-four, twenty-nine, thirty-six, forty-eight, fifty-nine, eighty, one hundred twelve, one hundred fifty-eight and two hundred days. Culture was strongly positive through eighty, negative at one hundred twelve days and thereafter. Animal was strongly positive through one hundred twelve, negative at one hundred fifty-eight days and thereafter. The demonstrated viability of the tubercle bacilli therefore lay somewhere between one hundred twelve and one hundred fifty-eight days or between three and two-thirds and five and one-third months. Again animal proved somewhat superior to culture, the former being positive in one instance where the latter was negative.

This series of tests began in January, 1938, and was continued through most of the month of June. Mean monthly temperatures were 61°, 57°, 58°, 62°, 63° and 65°F., respectively, with an average of 63°F. Mean monthly relative humidity values were 54, 71, 71, 74, 81 and 87 per cent, respectively, with an average of 73 per cent.

Experiment 4: Both naturally and artificially positive sputum was tested. The former was pooled from five fresh specimens and was estimated to contain 56,000,000 acid-fast bacilli per cc. so that the dose deposited in each case would

be 2,800,000. The latter contained 0.1 mg. moist culture per cc. or an estimated 20,500,000 microörganisms; 0.005 mg. or about 1,025,000 microörganisms per dose. Smears were made in a catalogue (not the same) containing firm, non-glossy paper. Culture was performed immediately, culture and animal inoculation at fourteen, thirty, forty-eight, fifty-six and eighty-four days.

For the natural tuberculous sputum, both culture and animal were strongly positive at fourteen days, but negative at thirty days and thereafter. For the artificial preparation, culture was strongly positive immediately, but negative at fourteen days and thereafter; whereas animal was positive at fourteen days, but negative at thirty days and in all subsequent tests. According to this experiment, then, the viability of the microörganisms was about the same in both sputa, that is, between fourteen and thirty days. However, the failure to get a positive culture from the artificial preparation at fourteen days suggests a somewhat shorter survival. The greater part of this test was completed in the month of July, 1938, during which the mean temperature was 70°F. and the mean relative humidity 83 per cent.

Experiment 5: Two different sputum preparations were used. The first was pooled from four fresh, naturally positive specimens and was estimated to contain 21,500,000 acid-fast bacilli per cc. or 1,075,000 per dose. The second was artificially positive and made to contain 0.1 mg. moist culture per cc. or 0.005 mg. (about 1,025,000 bacilli) per dose. Smears were made on 22 mm. square glass cover slips, stacked sheets of high grade bond paper, the dull, loose-textured pages of a novel and on the glossy pages of a popular magazine. All preparations were kept in the dark.

The results of culture and animal inoculation are shown in table 1. The tubercle bacilli lived longest in the cover-slip preparation where they were still demonstrable at one hundred forty-two days. Here, although the upper limit of life was not established, a negative guinea pig and a barely positive culture suggest it was closely approached. The maximum proven viability for novel and magazine preparations was the same, that is, ninety days and, so, almost as great. On the other hand, the microörganisms deposited on bond paper lived a relatively short time, not being recoverable at twenty-seven days.

Survival was definitely greater in the naturally positive than in the artificially positive preparations. Thus the maximum proven viability on cover slips was one hundred forty-two days for the former and only forty for the latter. In the novel and the magazine, the periods were ninety and sixty days respectively; on bond paper sixteen and zero. In the majority of cases animal inoculation proved to be the more sensitive method of recovery.

The period of the exposure extended through November and December, 1938, January, February and March, 1939. Mean monthly temperatures were 63°, 62°, 57°, 54° and 57°F., respectively, with an average of 59°F. Mean monthly relative humidity percentages were 41, 24, 63, 60 and 78, respectively, with an average of 53.

The essential data for all the experiments is given in table 2. The highest proven survival of tubercle bacilli was one hundred forty-two days in a natural

sputum suspension deposited on glass squares in experiment 5. The greatest viability on paper, between one hundred twelve and one hundred fifty-eight days in experiment 3, occurred where the highest per smear dose was employed, that is, 0.5 mg. Elsewhere smears from prepared suspensions contained 0.005 mg. or an estimated 1,025,000 bacilli (except in experiment 1 where the per smear dose is unknown but where the bacillary concentration of the suspension was the same); while smears from natural suspensions were estimated to

TABLE 1

Experiment 5

Exposure of naturally and artificially positive sputum in the dark

Begun October 28, 1938

DAYS	NATURALLY POSITIVE SPUTUM DOSE PER SMEAR: 1,075,000 ACID-FAST BACILLI							
	Cover Slips		Bond Paper		Novel		Magazine	
	Culture*	Animal†	Culture	Animal	Culture	Animal	Culture	Animal
0	++++		++++		++++		++++	
16	++++	++++	−	+++	++++	+++	++++	++++
27	+++	++++	−	−	++++	++++	++++	++++
40	++++	+++	−	−	++++	+++	++++	+++
60	++++	+++	−	−	+++	++++	++	++++
90	+++	+	−	−	++++	+++	−	+
142	+	−			−	−	−	−
	ARTIFICIALLY POSITIVE SPUTUM DOSE PER SMEAR: 0.005 MG. MOIST CULTURE OR 1,025,000 TUBERCLE BACILLI							
0	++++		++++		++++		++++	
16	−	+++	−	−	−	++++	−	+++
27	−	+++	−	−	−	+++	−	+++
40	−	+	−	−	++++	+++	−	+++
60	−	−	−	−	−	+++	−	+++
90	−	−	−	−	−	−	−	−
142					−	−	−	−

* Amount of growth after eight weeks of culture: + = 1 to 4 colonies; ++ = 5 to 20 colonies; +++ = 21 to 60 colonies; ++++ = 61 or more colonies; − = no growth.

† Amount of visceral tuberculosis: + = minimal at 2 months; ++ = minimal at 1 month; +++ = moderate at 1 month; ++++ = extensive at 1 month; − = none.

contain 575,000, 2,800,000 and 1,075,000 microörganisms in experiments 2, 4 and 5, respectively. Although these counts show considerable variation they are of the same order and roughly comparable.

Viability in preparations from natural or artificial suspensions in experiments 1, 2 and 4 was about the same, something between two weeks and two months. It was more specifically determined in experiment 4 as lying between two weeks and one month and in experiment 2 as between eighteen and twenty-three days. In experiment 5, on the other hand, except in the case of bond paper, the values

were not only much higher but those for natural sputum definitely surpassed those for artificial preparations. Thus for the former, the viability range was ninety to one hundred and forty-two days; for the latter, forty to ninety.

With the exception of bond paper preparations the shortest life spans for tubercle bacilli were in the spring (fifteen to sixty-one days: experiment 1);

TABLE 2

Summary

The results of exposure of tubercle bacilli in books, stacked paper and on cover slips

EXPERIMENT	DATE BEGUN	SPUTUM SUSPENSION	DOSE PER SMEAR	WHERE DEPOSITED	DAYS OF EXPOSURE	
					Tubercle bacilli alive at	Tubercle bacilli not recoverable at
1*	4- 5-37	Prepared†	Not known (0.1 mg. per cc. in suspension)	Blank tablet	15	61
				Catalogue	15	61
				Printed sheets‡	1	4
2	9- 9-37	Natural	575,000	Catalogue	18	23
3	1-19-38	Prepared	0.5 mg. (102,500,000)	Novel	112	158
4	7- 6-38	Natural	2,800,000	Catalogue	14	30
		Prepared	0.005 mg. (1,025,000)	Catalogue	14	30
5	10-28-38	Natural	1,075,000	Cover slips	142	
				Bond paper	16	27
				Novel	90	142
				Magazine	90	142
		Prepared	0.005 mg. (1,025,000)	Cover slips	40	60
				Bond paper	0	16
				Novel	60	90
				Magazine	60	90

Average of the mean monthly temperatures and relative humidity values: experiment 1, 63°F. and 77 per cent; experiment 2, 72°F. and 79 per cent; experiment 3, 61°F. and 73 per cent; experiment 4, 70°F. and 83 per cent; experiment 5, 59°F. and 53 per cent.

* Recovery by culture only. In all other experiments recovery was by both culture and guinea pig.

† A water suspension of tubercle bacilli was used in experiment 1 instead of sputum.

‡ Exposed to daylight. In all other cases preparations were kept in the dark.

in the fall (eighteen to twenty-three days: experiment 2); and in the summer (fourteen to thirty days: experiment 4). The longest life spans, on the other hand, occurred in the winter-spring (one hundred twelve to one hundred fifty-eight days: experiment 3); and in the fall-winter (sixty to ninety, ninety to one hundred forty-two days, etc.: experiment 5). If the average of the mean

monthly temperatures and relative humidity percentages are arrayed according to diminishing value we have:

Experiment 2	72°F. and 79 per cent
Experiment 4	70°F. and 83 per cent
Experiment 1	63°F. and 77 per cent
Experiment 3	61°F. and 73 per cent
Experiment 5	59°F. and 53 per cent

Thus the shorter life spans are associated with higher mean temperatures and higher relative humidity values.

DISCUSSION

These findings agree in general with those of a previous experience with tubercle bacilli deposited on glass cover slips (5). In both cases proven survival at room temperatures was not more than a few days in roomlight and from less than two weeks to about three and a half months in the dark. In both cases the period of recovery was extended when the dosage was increased, during the winter season and by animal inoculation. This suggests that, in general, paper and glass are equally favorable to the bacilli and that in at least some papers there is nothing very hostile toward them.

The unusually long viabilities in the novel and magazine of experiment 5 are not reasonably attributable to the type of paper since, in the same experiment, the microörganisms lived about as long on glass cover slips. On the other hand, their relatively short life on bond paper *is* significant and must be ascribed to some characteristic of the paper itself.

There is no evidence that printer's ink has an unfavorable effect since, in both experiments 5 and 1, the bacilli lived at least as long on printed as on blank paper.

The composition of papers and printing inks varies extensively. However, almost all papers contain wood pulp treated with sulfites (or alkalis) and subsequently bleached with chlorine (8). Washing and neutralizing agents are employed to diminish the residual chemical activity. More or less bleached cotton pulp may be added. Other variables are *sizings* of gelatin, rosin, alum, casein, starch, silicates, soaps, etc.; and *loadings* of kaolin, chalk, soapstone, etc. Printing inks are composed of pigments and varnishes. The former are usually prepared from lamp black with or without added indigo, prussian blue, etc. The latter frequently contain linseed oil, rosin and soap.

All the papers tested in these experiments had pH values between 5 and 6. This is well below the optimum level for culture of tubercle bacilli and possibly a factor in reducing their viability. Unneutralized remnants of sulfites, chlorine, wood acids and other chemicals might well be detrimental. A manufacturer's report showed the bond paper in question to contain, besides bleached wood and cotton pulp, sodium resinate, aluminum sulfate and corn starch. Aluminum sulfate may by hydrolysis form sulfuric acid. Starches as well as casein and gelatin which are often used in book papers are organic materials and conceivably protective to bacteria by their buffer and neutralizing qualities. It seems likely

that for most papers and printing inks active chemicals have been sufficiently removed or neutralized that little or no life-inhibiting quality remains.

The only visible explanation for the remarkably long periods of recovery in experiment 5 is the season of the year in which the exposures were made. As shown above, the average temperature and relative humidity during this period were lower than those for all the other experiments. We found previously (5) that tubercle bacilli on glass live much longer in the ice-box than at room temperature and it is likely that lowering the temperature favors viability. Furthermore it is known that the moisture content of paper varies widely with the relative humidity (9). Thus with a relative humidity of 40 per cent, the moisture content was 3.4 per cent; with a relative humidity of 80, the moisture content was 8.9 per cent, etc. Ionization and, hence, activity of any unstable chemicals present should increase with increased moisture and so enhance their injuriousness, if any, to the tubercle bacillus.

The apparent longer life of tubercle bacilli in naturally as compared with artificially positive sputum preparations of experiment 5 is interesting. The bacillary counts for the two suspensions were almost the same. Such counts, of course, are not very dependable. They are subject to considerable technical error. They do not include non-acid-fast tubercle bacilli. More important, they do not reveal the proportion of living bacilli. Other possible factors are differences in age and strain; the protein content of the sputum; and the presence of antibodies or other detrimental substances in the sputum medium.

Positive patients may contaminate the books and magazines they read by means of spray from the mouth and by contact with the hands or bed clothes. A droplet spray is emitted during talking, coughing or sneezing. The larger droplets, many of which are macroscopic, perhaps even up to drop size, will strike the pages and adhere. Hands may be contaminated from the mouth, from mouth wipes or handkerchiefs and, in some cases, through the habit of thumb or finger wetting (in the mouth) to facilitate turning the pages. Bed clothes may be contaminated by immediate contact with the mouth, by mouth spray, by contact with the hands and with the mouth wipes. Tubercle bacilli already dry when deposited in books should be readily detached and available for recovery by the subsequent reader. Moist deposits, that dry on the paper, however, because of the glue-like nature of dried sputum are probably quite tenacious. The proportion stirred up into dust when the pages are turned by a subsequent reader or that adhering to hands or bed clothing is probably small. In turn, a more or less small part of the dust will be breathed in and of the contaminating bacilli conveyed to the mouth by hands, food, etc. The thumb-wetter must reap a considerably larger harvest as moisture-loosened samples are conveyed directly from each page to the mouth. Furthermore, the same corners of the pages are likely to be favored by thumb-wetters both in deposit and recovery of bacteria.

To get some idea of the frequency of open coughing and thumb-wetting while reading, we distributed a questionnaire to all the patients at Barlow Sanatorium. These questionnaires were answered secretly. That is, they were unsigned,

folded and dropped into a ballot box. I believe, in the majority of cases, the answers were honest and accurate. Of 93 patients, 67 said they *never* coughed without covering their mouths while reading, 25 said they coughed *occasionally* and one *frequently*. One wrote that coughs sometimes come so suddenly there isn't time to cover the mouth. Eighty-one patients said they never indulged in thumb-wetting as a means of turning pages; 8 said they did it occasionally and 4 admitted doing it frequently. This shows that occasional uncovered coughing into books is fairly common even among supposedly trained sanatorium patients. No doubt a good proportion of the occasional coughs are of the "too sudden" variety. The thumb-wetting habit, as might be supposed, is rather uncommon.

Before making generalizations on the basis of our experiments it must be remembered that the conditions under which they were carried out were exaggerated. The amount of sputum smeared in the books was much larger than would be expected to be deposited by a tuberculous reader. The bacillary concentration of the sputum preparations was greater than that produced by all but the most strongly positive patients. Experimental recovery of each deposit was, presumably, nearly complete whereas the reader of a contaminated book recovers at most a small part of the contained bacteria. True, reader recovery is cumulative page by page on through the book. The experimentally determined survival periods should be maximal. The survival of tubercle bacilli in contaminated books in recoverable quantities should be well within the experimentally determined limits.

That contaminated books and magazines really cause tuberculosis is, of course, not certainly known. Lacking proof, they must be considered possible sources of infection. They are possible sources of infection for periods varying from two weeks to four or five months. In most cases, however, the danger period should be less than a month and probably not more than two or three weeks. During this time, I believe such books ought not be read by nontuberculous persons, including student nurses and sanatorium staff members. To be completely consistent, they perhaps ought not even be read by negative patients. Except as prescribed below, sanatorium patients should not be allowed to read and return books loaned by outside persons or libraries. Likewise, in general hospitals, books and magazines issued to tuberculosis wards and rooms should be segregated and not made available to the other patients. By the same token and with the same exceptions, it appears improper for a sanatorium library to be a part of a general circulating library system.

Sterilization of books is, as far as I know, impractical. Dry or moist heat as well as chemical agents penetrate the pages with difficulty while they damage bindings and paper. The effective use of ultraviolet lamps or sunshine would require the methodical exposure of each page. As indicated above, there is a simple and effective method for rendering contaminated books noninfectious. That is, *quarantine*. I believe a storage period of one month should in most, if not all, cases be sufficient. A fair proportion of library books no doubt remain on the shelves that long between loans. Books used by the more strongly positive patients might well be segregated into a special group and given more time

for good luck. A period of five months ought to insure complete safety in any case.

SUMMARY

1. Tubercle bacilli deposited in books and magazines were recoverable alive for from two weeks to three and one-half months. They were not recoverable at from three weeks to five months.

2. In general, they lived about as long on paper as on glass. They lived as long on printed as on blank paper. One type of paper was definitely inhibitory to the bacilli.

3. The period of recoverability was longer when the dose deposited was larger and during the winter season when average temperature and relative humidity were lowest.

4. Occasional uncovered coughing into books is fairly common among sanatorium patients. Thumb-wetting occurs, but is infrequent.

5. Books and magazines used by sputum-positive patients are possible sources of infection. They should not soon be read by nontuberculous persons.

6. Contaminated books ought, in most cases, be rendered safe and noninfectious by a quarantine period of one month.

SUMARIO

1. Al cabo de un período de dos semanas a tres meses y medio, todavía podían recobrarse vivos bacilos tuberculosos depositados en libros y revistas, pero no al cabo de períodos que variaron de tres semanas a cinco meses.

2. En general, los bacilos vivieron tanto tiempo en el papel como en el vidrio, y por igual en el papel impreso o en blanco. Hubo una clase de papel que manifiestamente inhibía los bacilos.

3. El período de recuperabilidad se prolongó más cuando la dosis depositada era mayor, y durante el invierno en que la temperatura media y la humedad relativa alcanzaba su mínimo.

4. Entre los enfermos del sanatorio no es raro que tosan de cuando en cuando en los libros sin taparse la boca. También se mojan en la boca el dedo pulgar, pero esto sí es raro.

5. Los libros y revistas empleados por enfermos con esputo positivo constituyen posibles focos de infección, de manera que no deben leerlos poco después sujetos no tuberculosos.

6. En la mayor parte de los casos, los libros contaminados deben cuarentenarse por un mes, para convertirlos en inocuos y no infecciosos.

REFERENCES

(1) Twitchell, D. C.: The vitality of tubercle bacilli in sputum, Tr. Nat. A. Prev. Tuberc., 1st annual meeting, 1905, p. 221.

(2) Arms, B. L., and Wade, E. M.: Variations in the longevity of tubercle bacilli from different individuals, Ibid., 8th annual meeting, 1912, p. 493.

(3) Soparker, M. B.: The vitality of tubercle bacilli outside the body, Indian J. M. Research, 1917, *4*, 627.

(4) POTTER, T. S.: Survival of oxygen and water deprival by tubercle bacilli, J. Infect. Dis., 1937, *60*, 89.
(5) SMITH, C. R.: Survival of tubercle bacilli, Am Rev. Tuberc., 1942, *45*, 334.
(6) KENWOOD, H., AND DOVE, E. L.: The risks from tuberculous infection retained in books, Lancet, 1915, *2*, 66.
(7) JACOBS, M. A., AND PETROFF, S. A.: Etiological studies of tuberculosis, Quart. Bull. Sea View Hosp., 1941, *7*, 33.
(8) Encyclopedia Britannica, 14th ed., 1932, Encyclopedia Britannica Inc., New York.
(9) JAHANS, Z. H.: Paper testing and chemistry for printers, 1931, Sir Isaac Pittman and Sons, Ltd., London.

MEDIA FOR TUBERCLE BACILLI[1, 2]

An Evaluation of Different Media for Diagnostic Cultures of Tubercle Bacilli

H. J. CORPER AND MAURICE L. COHN

Practically speaking, nutrient media have been developed for growing tubercle bacilli for two important purposes primarily: the first is to grow the bacilli in large amounts for the preparation of an important commercial product—tuberculin, and to obtain large amounts of bacillary bodies for scientific study. This, however, and the growth in heavy plants on numerous media rather confused the issue of the second and most important purpose, that of obtaining growth from very small plantings for diagnostic use. It is this latter phase of culturing tubercle bacilli with which this study is primarily concerned. Historically, this phase of cultural endeavors is marked by innumerable attempts without full understanding of the problem at hand. Part of the confusion may have resulted from attempting to equal the highly sensitive guinea pig by mimic rather than by following the strict quantitative evaluation of nutrient principle which was first pointed out definitely in 1927 (1, 2). The imitation of the guinea pig, however, so far as destroying contaminators is concerned, led to the introduction of both sulphuric and oxalic acid, which are practically innocuous to small numbers of bacilli (3). Oxalic acid is preferred for its stability in solution, purity and crystalline property. Prior to this, attempts were made to use formaldehyde, antiformin (or Labarraque's solution) otherwise known chemically as sodium hypochlorite, and finally sodium hydroxide, in 1915. Most of these reagents were lauded because of their solvent effect upon tissues and sputum or pus. This very fact, however, made them a possible destructive agent injuriously affecting small numbers of tubercle bacilli, not to mention the added disadvantage possessed by pure sodium hydroxide solutions of deteriorating by the absorption of carbon dioxide. Instability and toxicity toward small numbers of tubercle bacilli are the greatest drawbacks of these reagents. Aside from the nutrient medium itself, there are a number of other conditions that must be fulfilled to grow tubercle bacilli successfully from small plantings, and these have been studied variously and the results finally summarized as follows in 1936 (4).

1: Growth temperature—about 37.5°C. constantly maintained.
2: Absence of light.
3: Nutrient medium.
- a. Proper preparation and sterility (thirty minutes at 15 lbs. or three daily inspissations at 85° to 90°C. for one hour each).
- b. Adequate nutrient qualities.
  1. Potato (neutralized (5)).
  2. Egg yolk (6).
  3. Blood.
  4. Tissues.

[1] From the Research Department, National Jewish Hospital, Denver, Colorado.
[2] This investigation was aided by Mrs. Isabel Sewall, in memory of Dr. Henry Sewall.

4: Hydrogen ion concentration—about pH 6.5 to 7.0.
5: Isotonicity.
6: Maintain water and air balance (7).
  a. Enoughwater in medium.
  b. Paraffin impregnated cotton plug to prevent absorption of water from medium.
  c. Dry cork (not paraffined—moisture prevents satisfactory air permeability). The cork innerlined screw cap tube or bottle can be used satisfactorily (8) but rubber stoppers or caps prevent ready air access.
7: Elimination of secondary organisms from contaminated materials by sulphuric or oxalic acids (or other stable and safe reagents).
8: Absence of inhibitory dyes or chemicals in the medium (nontoxic or nonbacteriostatic dyes may be chosen to help in discerning early colonies more readily).

The fascination of multiple component nutrients for growing tubercle bacilli has its prototype in the well known "gunshot prescription" of by-gone days in clinical therapeusis. As a result, each year numerous papers appear on new culture medium combinations and modifications without warranted scientific tests. The importance of this subject is attested by reports from two committees which define culture methods for diagnostic purposes without adequate test. One of these modifies the report by suggesting their methods are "tentative." The earlier report (9, 10), from "the Referee and Associate for Tuberculosis and the Tubercle Bacillus for the Standard Methods Committee on Diagnostic Procedures and Reagents" of the American Public Health Association, recommends a confusing and dazzling array of "gunshot prescription" media on the basis of empiric routine specimen examinations, so that one is left wondering about the wide range of variety and is given no particular choice and with no obvious reason. They also recommend the use of rubber caps placed over a cotton plug. In 1942, the Committee on Standard Laboratory Procedure of the American Trudeau Society (11) recommended Loewenstein's medium as modified by Jensen and Holmes, Loewenstein's medium as modified by Wooley and later by Petrik, and Petragnani's medium as modified by Saenz. The variety of modifications speaks for itself and indicates a lack of reliably controlled scientific testing by the Committee. They also recommend rubber caps placed over cotton plugs. If we stop to analyze the media, they recommend asparagin, various buffer salts, potatoes or potato flour, whole egg and yolk in addition, and only one omits milk.

Of all the multiple essentials to assure the success of the cultural diagnosis, none would appear to be more important individually than that concerned with the selection and preparation of a proper nutrient capable of determining a positive culture from a few bacilli. For economy, as well as efficiency, it would appear only just that this nutrient should be as simply prepared as possible to retain its efficiency and yet it should not lack in essentials to achieve the desired results. Since there is only one criterion for the value of a nutrient medium for tubercle bacilli, it would seem that this criterion should be applied to each nutrient alone and in combination with its added constituents to determine their worth individually and conjointly. The selection of this criterion must be based necessarily on quantitative plantings to a point of practical extinction from a

standpoint of bacterial dilution. In all of our earlier studies, this criterion has been applied rigidly with the results recorded above. The irregularity of natural clinical tuberculous material completely excludes it from use in exact evaluation of nutrients. Recognizing this from our earlier work, Schwabacher (12) found that simple egg yolk media were superior to the whole egg or the complex Loewenstein or Petragnani media.

Even quantitative plantings, like all quantitative methods, have limitations which must be recognized. Since they are far superior to any "hit or miss" method and really are the only means available for accurate analysis, they offer the only plausible solution to a problem which has been so frequently approached unintelligently or circumvented entirely. In a mathematical theoretical evaluation of a hypothetical suspension of tubercle bacilli, Berg (13) recently showed that the disagreement between guinea pig and culture test may be caused by random sampling of varying numbers of bacilli in assumed equal doses and that this can be diminished or eliminated by concentrating the specimen. It may be pointed out that graded dilutions with fine suspensions if planted or inoculated in definite increments as tests are usually performed in the method as we use it; and when a definite number of tubes are planted, three or more for each dilution, error and false observations in culture tests are reduced. The factors involved in guinea pig tests, however, are not resolved so readily into simple form because virulence of the bacilli and individual resistance of the animals introduce added factors not concerned in culturing.

However, since no one except Schwabacher has exerted the effort to attain a quantitative evaluation of some of these media, we have felt that such an evaluation at this time might be warranted for its value alone and for the guidance of those who may study nutrients further for growing small numbers of tubercle bacilli diagnostically. In all quantitative tests to be recorded, fine suspensions and dilutions of tubercle bacilli were prepared according to the directions presented in 1936 (14). There are a number of procedures that can be used, but they must yield quantitative results in suitable control tests and assure the preparation of finely divided suspensions. Filtering of suspensions, so frequently advocated to remove lumps, is to be avoided.

YOLK MEDIUM IS SUPERIOR TO WHOLE EGG MEDIUM

In earlier studies it was found that the use of egg yolk was superior to whole egg in supporting growth from small plantings of tubercle bacilli as determined by speed of visible growth macroscopically and the dilution in which growth was still obtained. The white of egg alone proved a poor nutrient in comparison. The same was found to be the case with the poor nutrient quality of blood serum or plasma as compared with the corpuscular elements. Likewise, in earlier studies with both potato and egg media, the addition of nutrient broth was found unessential. Although the potato medium was originally recommended by us, we have found that the neutralization is not always performed accurately and that sometimes, in spite of the utmost precaution, laboratory technicians have found it difficult to avoid the preparation of irregular batches of medium. Since

the yolk medium is handled more easily and since it yields a slightly earlier though not as conspicuous growth for all practical purposes, it proves more desirable, even though the nutrient quality of properly prepared potato media is excellent.

In order to note this relation between the inspissated yolk and whole egg media with and without broth, dilution planting tests were performed using 4 strains of human tubercle bacilli with the results recorded in table 1.

The results recorded in table 1 definitely indicate that inspissated yolk-glycerol-water medium reveals an earlier growth of human tubercle bacilli planted in small numbers than does whole egg-glycerol-water medium. With

TABLE 1

*A comparison of the growth of a highly virulent strain of human tubercle bacilli (H160) on various egg media**

MEDIA	AMOUNT OF TUBERCLE BACILLI IN MG. PER CC. IN SUSPENSIONS USED FOR PLANTING CULTURE MEDIA			
	10^{-6}	10^{-7}	10^{-8}	10^{-9}
Yolk-glycerol-water	3**	3	3	3^{2***}
Whole egg-glycerol-water	3	5	5	5^{2}
Yolk-glycerol + broth†	3	3	4	0
Whole egg-glycerol + broth†	3	4	0	0
Yolk-glycerol + 4x broth††	6	5	5^{2}	0
Whole egg-glycerol + 4x broth††	5	5	5^{2}	0

* The results for this virulent strain of human tubercle bacilli and three other strains are essentially the same, so only this one strain is presented here to conserve space.

** The numeral indicates the number of weeks in which growth first appeared on the medium, three tubes being planted.

*** An exponent added to the numeral indicates the number of tubes which revealed a positive growth at the time indicated by the numeral.

† Broth was added to the medium in ordinary single strength and in amount of 25 per cent of the total weight of the medium.

†† 4x broth was added to the medium in four times the usual concentration and in amount of 25 per cent of the total weight of the medium.

some strains of human tubercle bacilli, the yolk-glycerol-water medium definitely reveals growth with smaller plantings than does the whole egg medium. It is to be noted also that the addition of the broth adds nothing to the efficiency of the egg media for disclosing early growth or in small plantings. As a matter of fact, broth was found in some cases to be definitely retarding to the growth of some strains. Likewise, asparagin added in place of broth did not benefit the egg or egg-yolk media.

PLAIN YOLK MEDIUM IS SUPERIOR OR EQUAL TO ANY MULTIPLE MIXTURE MEDIUM

It is impossible to record here the comparative trials with all the multiple mixture media and their modifications in which we used graded plantings of small numbers of tubercle bacilli. Since the general trend of results is not

affected materially by adding additional good nutrients, such as mixing potato and egg, blood and egg, etc., the results are given with a few of these multiple mixture media tried coincidently with the simple yolk medium. The results presented were chosen at random with a single strain of tubercle bacilli, but in each comparative test at least four different strains were used (see table 2).

COMPOSITION OF MULTIPLE MIXTURE MEDIA USED

Medium 1: Loewenstein (15) (recommended by MacNabb (10)).

(1) Twenty eggs carefully cleansed by immersion for one-half hour in tepid soapy water to which is added 5 per cent sodium carbonate.

(2) Asparagin solution: asparagin (Merck) 3 g.; K_2HPO_4 (potassium phosphate, Merck) 1 g.; sodium citrate 1 g.; magnesium sulphate 1 g.; pure glycerol 30°B. 60 cc.; distilled water 1,000 cc. This solution is sterilized for two hours in flowing steam. It is very stable.

TABLE 2

A comparison of the growth of small numbers of human tubercle bacilli (H7) on the simple egg-yolk medium as compared with two common multiple mixture media†

MEDIUM	AMOUNT OF TUBERCLE BACILLI IN MG. PER CC. IN SUSPENSION PLANTED ON THE MEDIUM			
	10^{-6}	10^{-7}	10^{-8}	10^{-9}
Inspissated yolk	3*	4	4	4^{2**}
Petragnani	3	4	6^{2}	0
Loewenstein	3	4	4^{2}	4^{1}

* The numeral indicates the weeks in which the earliest growth could be seen macroscopically.

** The exponent following the numeral indicates the number of tubes of medium (of 3 planted) in which growth resulted.

† Three other strains of tubercle bacilli gave essentially these same findings with only slight variations.

(3) Potato starch (flour).

(4) Congo red 2 per cent aqueous solution sterilized in autoclave for fifteen minutes.

(5) Malachite green 2 per cent aqueous solution sterilized in flowing steam for two hours.

To 600 cc. of the asparagin solution one adds 10 cc. of a 50 per cent solution of potato starch (flour) and 60 cc. of sterile tomato juice. This mixture is heated for two hours on a water bath. After cooling to 50°C., 16 eggs are added and then the yolks of 4 eggs. Then the mixture is actively stirred and 20 cc. of congo red (or malachite green) are added. After stirring, it is filtered through four layers of gauze. Then it is tubed. Coagulation is produced by heating to 75° to 80°C. in flowing steam. The tubes are carried to the oven and next day are again heated for two hours at 75° to 80°C. To cap the tubes use cellulose. The culture medium should be prepared oftener than every two weeks and kept in the dark.

Medium 2: Petragnani's medium (16) (recommended by MacNabb (10)).

"Preparation of medium:

Milk	160 cc.
Potato starch (flour)	6 gs.
Peptone	1 g.

Place these ingredients in a liter flask with pieces of peeled potato the size of a hen's egg. Take the flask by the neck and put it in boiling water, shaking vigorously. When it has formed a colloid dough, stop shaking and leave in the boiling water bath for one hour. Take it out and leave until the temperature is down to 60°C. Add 4 whole eggs and one yolk. It is not necessary to sterilize the flask or milk, or to treat the eggshells. Now add glycerol, 12 cc. and malachite green, 2 per cent aqueous solution, 10 cc. Stir until it becomes a homogeneous mass and filter the mass through sterile gauze into a sterile flask; fill into sterile tubes (20 cm. by 22 mm.) or plates using 12 to 15 cc. of medium for each. Solidify in an inspissator in the following manner: place the tubes or plates in the inspissator when it is still cold, bring it slowly to a temperature of 85°C., keep it at this temperature for twenty-five to thirty minutes, and leave to cool. This treatment is usually sufficient to solidify and to sterilize the medium, but its nutritive properties are not damaged by a tyndallization of fifteen minutes at 80°C. the first day and ten minutes at 75°C. for two successive days (10)."

Medium 3: Inspissated egg yolk medium (6).

This medium, described in 1933, is prepared as follows: Fresh eggs, the shells having been cleaned by washing if they appear dirty, are broken and the white and yolk separated, the yolk being collected in a clean tared beaker. To 100 g. of yolk are added 33 cc. clear tap water and 4 g. of pure glycerol. This is mixed well by stirring with a rod; and after passing through several layers of clean gauze, the mixture is tubed. The medium is inspissated at 85°C. for one hour the first day and at 90°C. for one hour each on the second and third days. (Autoclaving for fifteen minutes may be used instead, provided a suitable autoclave is available which obviates bubbling of the medium.)

The sterilized medium may be preserved in the refrigerator for months by sealing each tube with a solid rubber stopper, or, if screw cap tubes are used, a small wide rubber band around the edge will prevent evaporation and drying of the medium, although the cork inner liner itself prevents this to a marked degree. The rubber stopper and rubber band *must not be used* during cultivation of the tubercle bacilli.

The results of a comparison of the three media described above using graded plantings of tubercle bacilli are recorded in table 2.

It is obvious from the results recorded in table 2 that the simple inspissated egg-yolk medium equals in efficiency any multiple mixture medium thus far devised for the diagnostic culture of small numbers of tubercle bacilli. Such conclusion is gauged from the results of comparative tests using the only logical method for such evaluation, that of quantitative plantings from fine suspensions of tubercle bacilli.

SUMMARY AND CONCLUSIONS

1. In comparative tests using quantitative evaluation, a simple inspissated egg-yolk medium described in 1933 was found equal in efficiency to any multiple mixture medium thus far described for growing small numbers of tubercle bacilli.

2. The predilection for well developed colonies may be misleading when judging the efficiency of diagnostic culture media for tubercle bacilli, since the addition of potato adds nothing to the efficiency of the egg medium but may only yield more voluminous and elevated final colony growth.

3. Heavy plantings or the use of routine empiric natural specimens are to be avoided as a gauge for the diagnostic value of a medium.

4. Multiple mixture media are to be avoided for diagnosis because they are extravagant, time consuming in preparation and redundant. If such media are advocated, they should be tested by using the individual ingredients as well as comparing them with the variously combined mixtures to show that such mixtures really merit the claims advanced for them.

5. A good illustration of a redundancy in diagnostic media is presented in demonstrating that broth adds nothing to the already high efficiency of an inspissated egg-yolk medium.

SUMARIO Y CONCLUSIONES

1. En las pruebas comparadas que utilizan la avaluación cuantitativa, un medio sencillo de yema de huevo espesada descrito en 1933, resultó igual en eficacia a cualquiera de los medios combinados múltiples descritos hasta ahora para cultivar pequeñas cantidades de bacilos tuberculosos.

2. La predilección hacia las colonias bien desarrolladas puede conducir a extravíos al juzgar la eficacia de los medios diagnósticos de cultivo para los bacilos tuberculosos, dado que la adición de patata en nada acrecienta la eficacia del medio de huevo, y lo único que puede hacer es rendir al final colonias más voluminosas y elevadas.

3. Al juzgar el valor diagnóstico de un medio, hay que evitar las siembras intensas o el empleo de ejemplares naturales empíricos como norma.

4. Hay que evitar el empleo de medios mezclados múltiples, pues resultan costosos, hacen perder tiempo en la preparación, y son innecesarios. Si se recomiendan estos medios, deben comprobarse utilizando los ingredientes separados, así como comparándolos con varias mezclas combinadas para confirmar si estas mezclas realmente merecen los elogios que se les tributan.

5. Un buen ejemplo de derroche en los medios de diagnóstico lo ofrece la demostración de que el empleo de caldo nada agrega a la eficacia ya elevada de un medio de yema de huevo espesada.

REFERENCES

(1) CORPER, H. J., AND UYEI, NAO: The isolation of tubercle bacilli from contaminated tuberculous materials, Am. Rev. Tuberc., 1927, *16*, 299.

(2) CORPER, H. J., AND UYEI, NAO: The cultivation of tubercle bacilli. An improved method for isolation from tuberculous materials, J. Lab. & Clin. Med., 1928, *13*, 469.

(3) CORPER, H. J., AND UYEI, NAO: Oxalic acid as a reagent for isolating tubercle bacilli and a study of the growth of acid-fast nonpathogens on different mediums with their reaction to chemical reagents, J. Lab. & Clin. Med., 1930, *15*, 348.

Additional observations on isolating tubercle bacilli: The oxalic acid reagent for primary culture, Am. J. Clin. Path., 1931, *1*, 135.

(4) CORPER, H. J.: The cultivation of tubercle bacilli, Am. J. Technol., 1936, *2*, 157.

Modern bacteriologic methods prove invaluable in army tuberculosis survey, Bull. Am. Acad. Tuberc. Physicians, 1941, *5*, 121.

(5) CORPER, H. J., AND UYEI, NAO: A simple glycerol water crystal violet potato cylinder medium for diagnostic cultures of tubercle bacilli, Arch. Pathol., 1929, *7*, 835.

(6) Corper, H. J., and Cohn, Maurice L.: The nutrient quality of eggs for growing tubercle bacilli, Am. J. Hyg., 1933, *18*, 1.

(7) Corper, H. J., and Cohn, Maurice L. Maintaining water and air balance during prolonged incubation, J. Lab. & Clin. Med., 1934, *19*, 899.

(8) Corper, H. J.: A simple procedure for the diagnostic culture of tubercle bacilli, Ibid., 1938, *23*, 1195.

(9) MacNabb, A. L.: Cultural methods of isolation of tubercle bacilli, Am. J. Pub. Health, 1936, *26*, 619.

(10) Tentative Methods for the Cultivation and Isolation of Tubercle Bacilli and the Production of Tuberculin, Supplement to Am. J. Pub. Health, 1936, *26*, 188; also, Am. Pub. Health A. Year Book, 1935–1936, pp. 188–192.

(11) Report of the Committee on Standard Laboratory Procedure-Minimum Laboratory Standards, Am. Rev. Tuberc., 1942, *45*, 103.

(12) Schwabacher, Herta: A comparison of different media for the growth of the tubercle bacillus, Tubercle, 1937, *18*, 199.

(13) Berg, Wm. N.: Guinea pig inoculation and culture. Disagreement between the two methods due to random sampling, Am. Rev. Tuberc., 1941, *44*, 757.

(14) Corper, H. J., and Cohn, Maurice L.: A mechanical device for preparing fine suspensions of tubercle bacilli and other microorganisms, J. Lab. & Clin. Med., 1936, *21*, 428.

(15) Loewenstein, E.: La methodé d'hemoculture du virus tuberculeux et ses résultats, Ann. Inst. Pasteur, 1933, *50*, 161.

(16) Petragnani, G.: Terreno e tecnica per l'isolamento in cultura pura dei B. di Koch dagli escreati a da altri materiali tubercolari, Atti d. r. Accad. d. fisiocrit. in Siena, 1926, *1*, 177.

SILICON DIOXIDE IN GUINEA PIG INOCULATION FOR TUBERCULOSIS[1]

HARRIETT HOLLON, MARIAN SPRICK, ELIZABETH CONROY AND ELIZABETH WILSON

A rapid and accurate method of laboratory diagnosis of tuberculosis has been desired by both clinicians and laboratory workers over a period of many years. Various methods have been tried in an attempt to shorten the time necessary for a positive diagnosis. deSchweinitz and Dorset (1) considered silica a favorable element for the development of tubercle bacilli. Gardner (2) found that guinea pigs infected with tubercle bacilli and then exposed to granite dust developed more tubercles than those not exposed to dust. Pickof (3), making a preliminary injection of colloidal silicon dioxide into guinea pigs before the inoculation of a diagnostic specimen, was able to demonstrate acid-fast organisms in aspirated material as early as ten to twelve days after inoculation. Woolsey (4) discovered that, when tuberculous material was inoculated subcutaneously into the shaved side of the abdomen of a guinea pig, nodules appeared within seven to twenty-one days. She also found that twenty days was the average time elapsing before positive autopsies were obtained. Heimi de Balsac *et al.* (5) found that the influence of silica in culture media for tubercle bacilli was negligible.

A controlled study was instituted to test the practicability of Pickof's method as a diagnostic procedure. The close association of the sanatorium and laboratory aided in the correlation of information.

MATERIALS AND METHODS

The diagnostic specimens submitted for animal inoculation for *M. tuberculosis* included sputa, pleural fluids, urines and miscellaneous transudates and exudates. The methods used in the preparation of specimens for animal inoculation conformed with procedures of the Michigan Department of Health, Bureau of Laboratories. In brief, they were as follows:

Sputa: This group consisted of single, and three to seven day pooled specimens. The entire specimen was transferred to a sterile centrifuge tube and an equal volume of Hanks' (6) solution added. The specimen was shaken thoroughly, allowed to digest at 37°C. for thirty minutes, neutralized with 2.5 normal hydrochloric acid and centrifuged at approximately 2,000 r.p.m. for ten minutes. The supernatant fluid was decanted and a part of the sediment stained for tubercle bacilli by Cooper's modification of the Ziehl-Neelsen method. The remaining sediment was resuspended in a small amount of saline and then divided into three portions, one for routine guinea pig inoculation, one for a guinea pig which had been inoculated previously with silicon dioxide and one for culture.

Urines: The entire specimen of urine was centrifuged and the supernatant fluid decanted. A Gram stain and an acid-fast stain were made of the sediment, which was also

[1] From the Michigan Department of Health, Bureau of Laboratories, Powers Division. In coöperation with Pinecrest Sanatorium, Dr. J. W. Towey, Director, Powers, Michigan.

cultured on blood agar and on Endo's medium. If no growth was obtained, the sediment was used for animal inoculation and cultures. Whenever growth was found on preliminary culture, 5 cc. of 3 per cent hydrochloric acid, containing brom-thymol-blue as an indicator, were added to the sediment. The material was shaken and allowed to stand for two hours at room temperature. The specimen was then neutralized with 3 per cent sodium hydroxide and centrifuged at approximately 2,000 r.p.m. for ten minutes. The supernatant fluid was decanted and the sediment resuspended in 2 to 3 cc. of sterile saline. This material was used for animal inoculations and cultures.

Pleural fluids: All fluids or serous specimens were centrifuged. If a web was present, it was ground in a sterile mortar. A Gram stain, an acid-fast stain and a culture for organisms other than the tubercle bacillus were made on all specimens. If no growth was obtained, the centrifuged sediment or ground-up web was resuspended in 3 cc. of pleural fluid and used for animal inoculations and cultures. Whenever growth was present on preliminary culture, either the centrifuged sediment or the ground-up web was treated in the same manner as the urine specimens.

Miscellaneous transudates and exudates: In general, these specimens were subjected to the same procedures used for pleural fluids.

Animal inoculations: Routine method: Guinea pigs weighing 250 to 300 g. were used. Approximately 1.0 cc. of the resuspended sediment was inoculated into the bruised inguinal lymph nodes of a guinea pig.

Silicon dioxide method: Washed and ignited sand was ground in a mortar until an amorphous powder was obtained. One-half gram of the powder was placed in a small sterile jar and 10 cc. of boiling sterile saline were poured over it. The suspension was shaken well and allowed to cool before using. One cc. of the silica suspension was injected subcutaneously into the plucked flank of a guinea pig, using a sharp 16 gauge needle on a 5 cc. syringe. Two to three minutes after the injection of the silica suspension, the concentrated diagnostic material was inoculated through the same puncture wound and into the same subcutaneous area as the silicon dioxide. The skin puncture was covered with collodion.

Aspirations: During the first part of the experiment aspirations were made only from the firm indurated area developing in the guinea pigs injected with silicon dioxide. For this procedure a 16 gauge needle on a 5 cc. syringe was inserted into the area. The needle was moved under the skin in various directions and the plunger pulled. The material obtained was placed on a slide and stained for acid-fast organisms. If no acid-fast organisms were found, a second aspiration was made a few days later. In some instances 3 or 4 aspirations were made. During the latter part of the study aspirations were made also on the animals injected by the routine method if nodules developed.

Observations and autopsy: All inoculated pigs were examined every few days and their general condition and the presence of any glandular enlargement recorded. At the end of the six weeks' observation period animals were killed and autopsied. The lymph nodes in the region of inoculation, retroperitoneal nodes, liver and spleen were examined. Organs showing lesions were removed and stained preparations made and examined for acid-fast organisms. If these were found, a positive report for *M. tuberculosis* was made. In some instances histological sections and cultures for *M. tuberculosis* were prepared from the lesions of the silica-injected animals.

RESULTS

Three hundred sixty-seven specimens were inoculated into guinea pigs in duplicate, one animal having been injected two to three minutes previously with

1.0 cc. of colloidal silicon dioxide. Three hundred twenty-two aspirations were made on 191 silica-injected guinea pigs. The results of these aspirations and the respective autopsy findings are given in table 1.

Of the 367 silica-injected guinea pigs, material was aspirated on one or more occasions from 185, no aspirations were made from 176, and unsuccessful attempts were made to aspirate 6. In 92 instances acid-fast organisms were

TABLE 1

Silicon dioxide injected guinea pigs—aspiration and autopsy results

RESULTS WITH ASPIRATED MATERIAL FROM SILICON DIOXIDE INJECTED PIGS	NUMBER OF GUINEA PIGS	NUMBER OF ASPIRATIONS		NUMBER OF AUTOPSIES	
		Positive	Negative	Positive	Negative
Positive, only one aspiration	77	77	0	70	7*
One or more negative aspirations followed by a positive aspiration	25	25	42	22	3
All negative aspirations	83	0	172	3	80
Unsatisfactory aspirations	6	0	0	6	0
Guinea pigs not aspirated	176	0	0	6	170
Totals	367	102	214	107	260

* One positive culture.

TABLE 2

Comparison of positive aspirations on silica injected and routine guinea pigs

TYPE OF SPECIMEN	NUMBER	SILICON DIOXIDE INJECTED ANIMALS		ROUTINE ANIMALS	
		Positive aspirations	Average number of days between injection and aspirations	Positive aspirations	Average number of days between injection and aspiration
Pleural fluids	16	12	27	4	27
Urines	20	17	21	12	21
Sputa					
Slide negative	11	8	32	1	13
Slide positive	20	20	13	15	20
Miscellaneous fluids	4	1	15	0	0
Totals	71	58	20.6	32	20.2

demonstrated in aspirated material and tuberculous lesions were found at autopsy. Fifteen additional animals were positive only at autopsy. Of especial interest were the 10 positive aspirations from guinea pigs in which no tuberculous lesions were demonstrated at autopsy. These will be referred to later.

As was stated previously, after this study had been in progress for several months, the routinely treated pig as well as the silicon dioxide-injected animal

was aspirated when a definite nodule or local inflammation was present. It does not follow, however, that the silicon dioxide-injected guinea pig and the corresponding routine animal were aspirated simultaneously. Frequently, the silicon dioxide-injected animal developed an indurated area while the other did not, and vice versa. Ninety-four aspirations were made on 63 routine guinea pigs, of which 32 were positive. The findings with regard to acid-fast organisms in aspirated material and the average length of time elapsing between inoculation and aspiration are given in table 2.

Tubercle bacilli were demonstrated in aspirated material from 58 guinea pigs injected with silicon dioxide and specimen, and from 32 guinea pigs injected with specimen alone. The average number of days after inoculation before positive aspirations were obtained was the same in both groups, approximately twenty.

The autopsy results on 367 guinea pigs inoculated in duplicate are summarized in table 3.

TABLE 3

Comparison of autopsy results with respect to tuberculous lesions in silicon dioxide and routine guinea pigs

RESULT	NUMBER	PER CENT
Positive by both methods	91	25.9
Positive with silicon negative with routine	7	2.0
Positive with routine negative with silicon	4	1.1
Negative by both methods	250	71.0
Total	352	100.0
Animal by one method died of intercurrent infection	15	

Table 3 reveals that 25.9 per cent of the animals inoculated were positive by both methods, 2.0 per cent by the silicon dioxide alone, 1.1 per cent by the routine method and 71.0 per cent were negative by both methods. Fifteen animals from one group or the other died of intercurrent infection.

COMMENT

In the silicon dioxide-injected animal, in general, we did not demonstrate acid-fast organisms in ten to twelve days as reported by Pickof. The average length of time elapsing between injection of specimen and positive slide examination of aspirated material was approximately twenty days. In several instances guinea pigs inoculated with silicon dioxide and positive sputum could be aspirated as early as the eighth day and acid-fast organisms were found in the aspirated material. However, the animals had been injected with material heavily loaded with tubercle bacilli and the aspirated bacilli may very well have represented the original inoculum rather than organisms multiplying in the lesion.

The marked difference between the number of positive aspirations, 58 in the

silicon dioxide series compared with 32 in the routine series, as shown in table 2, indicates that the presence of silicon dioxide aids in the development of local lesions and the multiplication of the tubercle bacillus. This also was demonstrated in the series of sputa with slide examinations positive for *M. tuberculosis*. There were 20 positive aspirations made in the silicon dioxide series in comparison with 15 in the routine series. However, when it was possible to obtain positive aspirations in the routine series, the average time required was the same as that with the silica-injected animals.

Ten silicon dioxide-injected animals, from which acid-fast organisms were found in aspirated material, showed no tuberculous lesions at autopsy. Case histories were available on 7 of the 10 patients from whom these specimens were obtained. There was one patient suspected of having incipient pulmonary tuberculosis, whose previous and subsequent sputum examinations were negative. There were 2 cases of silico-tuberculosis, one far advanced, the other a reinfection type of tuberculosis, neither with positive sputum. There were 2 cases of active tuberculosis with positive sputa. A positive culture for *M. tuberculosis* was obtained on the specimen of sputum submitted by one of these. A pleural fluid with the characteristics of tuberculous fluid was submitted from a patient with incipient pulmonary tuberculosis. No acid-fast organism were found on direct examination, and the culture for *M. tuberculosis* was also negative. The routine animal inoculated with this specimen died before the usual incubation period was completed. A faecal sample was submitted from a patient having far advanced pulmonary tuberculosis arrested by thoracoplasty. At the time of admission there was a question of tuberculous enteritis. Subsequent faecal specimens revealed no acid-fast organisms.

The fact that more aspirations were made on silica-injected animals than on the routine group suggests that silicon dioxide is an aid in producing local lesions so that aspirations can be made more easily. However, the results do not justify a positive report for *M. tuberculosis* being based on a slide examination of aspirated material alone, since in 10 instances such findings of acid-fast organisms were not confirmed at autopsy. The criterion for the laboratory diagnosis of tuberculosis is still the development of tuberculous lesions in the animal rather than the presence of acid-fast organisms in the aspirated material.

SUMMARY

Three hundred sixty-seven specimens were inoculated into guinea pigs in duplicate.

Three hundred twenty-two aspirations of lymph nodes were made on inoculated guinea pigs that had received silicon dioxide with the inoculum, of which 32 per cent were positive. Ninety-four aspirations were made on the routine animals of which 34 per cent were positive.

Of the total number of guinea pigs inoculated in duplicate, 25.9 per cent were positive by both methods, 2.0 per cent by the silicon dioxide method only and 1.1 per cent by the routine method only.

While silicon dioxide aids in the development of tuberculous nodules, the results suggest caution in its application to routine procedure.

SUMARIO

Inoculáronse en cobayos por duplicado 367 ejemplares de esputo.

En los cobayos inoculados que habían recibido bióxido de silicio con el inóculo se realizaron 322 aspiraciones de los ganglios linfáticos, resultando positivas 32 por ciento. Ejecutáronse 94 aspiraciones en los otros animales, resultando positivas 34 por ciento.

De todos los cobayos inoculados por duplicado, 25.9 por ciento resultaron positivos con ambos métodos: 2.0 por ciento solamente con la técnica del bióxido de silicio, y 1.1 por ciento solamente con la técnica corriente.

Aunque el bióxido de silicio fomenta la producción de nódulos tuberculosos, el resultado indica la necesidad de mostrar cautela al aplicar esa técnica al procedimiento corriente.

REFERENCES

(1) deSchweinitz and Dorset: Mineral constituents of the tubercle bacilli, J. Am. Chem. Soc., 1898, *20*, 618.

(2) Gardner, Leroy U.: Studies on the relation of mineral dusts to tuberculosis, Am. Rev. Tuberc., 1920, *4*, 734.

(3) Pickof, F. L.: The diagnosis of tuberculosis in ten to twelve days by guinea pig inoculations, Am. J. Clin. Path., 1939, *9*, 339.

(4) Woolsey, Carrie I.: A more rapid method of guinea pig inoculation for the diagnosis of tuberculosis, J. Lab. & Clin. Med., 1939, *24*, 855.

(5) Heimi de Balsac, H. F., Fernbach, E., and Rullier, G.: La silice exerce-t-elle une influence sur le dévélopement et la virulence du bacille tuberculex, Bull. Acad. de méd., Paris, 1940, *123*, 365.

(6) Hanks, J. H., Clark, H. F., and Feldman, H.: Concentration of tubercle bacilli from sputum by chemical flocculation methods, J. Lab. & Clin. Med., 1930. *23*, 736.

CLINICAL NOTES

FENESTRATION OF THE FIRST THORACIC RIBS[1]

Its Roentgenographic Confusion with Lung Cavitation

DOUGLAS S. KELLOGG[2] AND JOSEPH F. LINSMAN[3]

The differentiation of thoracic rib anomalies from lesions of the lung parenchyma is ordinarily not difficult for the experienced roentgenologist. However, the error is made in spite of the warnings of the literature that deal with the subject. The dilettante who is prone to rely on his own judgment in his interpretation of the chest has no doubt often been confused by bifid or forked ribs, synostosis of ribs, flared ribs, rhomboid fossae of the clavicles and other bone anomalies. These have no doubt been interpreted as organic lesions by many.

This report deals with the congenital anomaly of fenestration of the sternal extremities of the first thoracic ribs. This is apparently an uncommon anomaly, and yet it is one concerning which there should be cognizance. As shown in the case to be reported, it can easily be confused with cavitation within the lung parenchyma. In our patient this anomaly was diagnosed as pulmonary tuberculosis with cavitation by a well known department of radiology. Neither Brailsford (1) nor Köhler (2) in their books mention the condition among rib anomalies. The origin of the fenestrated rib is probably the result of a fusion of the anterior extremities of the commoner bifid or forked rib.

The bifid rib is not the condition with which this report is concerned. It is certainly much less confusing unless, as Sweany (3) has pointed out, there is underlying increased density due to a pathological lung process when the shadow formation could be confused with cavities, pleural blebs, etc. Sweany referred to the forked or bifid rib as fenestrated, and this is true if one considers the costocartilage as completing the fenestration. However, only if the costocartilage calcifies will such a rib give rise to a complete annular shadow on the roentgenogram. Our patient actually showed fenestration of the bony ribs themselves.

The differential diagnosis should be easy. It is only to be confused with cavity, bulla or bleb formation. One expects to see a definite wall around a lung cavity as well as infiltration or fibrous strands leading from the hilum to this region. However, even with these features lacking, and particularly with prominent vascular markings, the possibility of error is present. Stereoscopic views, though very helpful, may not be decisive in diagnosis. The use of the apical view with projection of the anterior portions of the first ribs away from

[1] From the Roentgenological Service, William Beaumont General Hospital, El Paso, Texas.

[2] Lieutenant Colonel, Medical Corps, U. S. Army.

[3] Major, Medical Corps, U. S. Army.

overlying shadows and into a different obliquity as was done in this case (figures 1 and 2) is definitely diagnostic. The bilateral occurrence of the anomaly is important in distinguishing it from other conditions.

CASE REPORT

G. I., a female, thirty-three, entered William Beaumont General Hospital on August 15, 1941 because of acute alcoholism. Her past history was essentially negative, except that in October, 1940 she was sent to a large county hospital because of weight loss, dry cough and chest pain. There, a chest roentgenogram was made and she was told

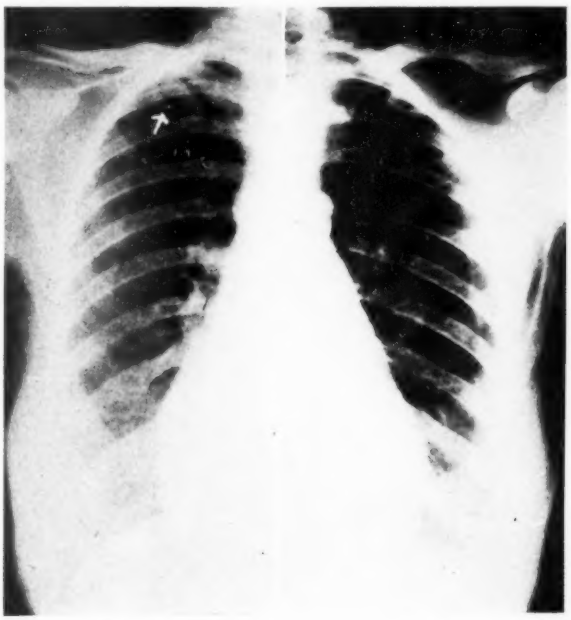


FIG. 1 FIG. 2

FIG. 1. Standard postero-anterior view of chest. Arrow points to the rib fenestration which simulates a cavity in the apex in this view.

FIG. 2. Special view made with the X-ray tube angled at 65 degrees towards the head and with the central ray projected antero-posteriorly at the level of the midportion of the sternum. The fenestration in the anterior portion of the first thoracic rib is now obvious.

that she had pulmonary tuberculosis with cavitation in the left apex. At that time she had been partaking of alcoholic beverages in excess and had been smoking about a half package of cigarettes daily.

She entered William Beaumont General Hospital after an alcoholic debauch lasting four days. Roentgenographic studies of the chest were made because of the patient's history of tuberculosis of the lung with cavitation. The chest was negative except for annular shadows measuring about 1 cm. in diameter in each apical region near the anterior extremities of the first ribs. Special apical views proved these to be true fenestrations of the ribs.

SUMMARY

1. A case of fenestration of the sternal extremities of the first thoracic ribs is reported.

2. This anomaly may simulate an intrapulmonary lesion and should be distinguished from it.

SUMARIO

1. Preséntase un caso de fenestración de los extremos esternales de las primeras costillas torácicas.

2. Esta anomalía puede simular una lesión intrapulmonar, de la cual debe ser diferenciada.

REFERENCES

(1) Brailsford, James F.: The Radiology of Bones and Joints, William Wood & Co., Baltimore, 1935.

(2) Köhler, Alban: Roentgenology, William Wood & Co., Baltimore, 1935.

(3) Sweany, Henry C.: A note on shadows of fenestrated ribs in roentgenograms, Am. J. Roentgenol., 1932, *28*, 541.

TUBERCULOSIS OF THE OESOPHAGUS[1]

ALBERT GUGGENHEIM, LOUIS ROTENBERG AND HERMAN I. LAFF

Tuberculosis of the oesophagus in any form is such a rare occurrence that textbooks commonly refer to it as a remote possibility not having any practical significance. Exhaustive autopsy statistics have shown that of all organs the oesophagus is least commonly involved in tuberculosis. Tuberculous lesions are more common even in the stomach.

In an excellent review of the literature Lockard (2) found that, of 103 cases of oesophageal tuberculosis reported up to 1912, only 69 could be considered as completely valid. In 44 of these cases a tuberculosis of the mediastinal lymph nodes accompanied the oesophageal lesions. In only 7 cases analyzed by Lockard was there evidence of a generalized (chronic haematogenous) tuberculosis. On the other hand it has been demonstrated that tuberculosis of the oesophagus is frequently associated with intestinal tuberculosis, which usually results from direct inoculation of bacilli in swallowed sputum. It should, however, be emphasized that intestinal and laryngeal tuberculosis is not always due to an intracanalicular dissemination but may be the result of a lymph or blood stream infection. Only in recent years has this problem received special attention, particularly in cases in which a laryngeal lesion preceded a clinically manifest pulmonary tuberculosis.

The pathogenesis of tuberculosis of the oesophagus was first classified by Flexner (1) in 1893 as follows:

1: By continuity of tissue from: (*a*) vertebral caries; (*b*) tuberculous mediastinal lymph nodes; (*c*) extension of pharyngeal ulcers into the oesophagus.
2: Due to a preëxisting lesion or stricture due to caustics, carcinoma, thrush.
3: Infection by direct inoculation of sputum, or as a result of general dissemination of tuberculosis.

The localization of the tuberculous lesion in the oesophagus manifestly depends to a large degree on the mode of infection. Where infection is by direct inoculation or by general dissemination, any part of the organ may be involved. Ulcers occur with equal frequency in the upper and lower thirds of the oesophagus. Where a predisposing lesion has an important rôle in the pathogenesis, its location will determine the site of the secondary tuberculous infection. Extension from the pharynx involves the upper oesophagus. Secondary involvement due to Pott's disease of the spine or to caseous disease of mediastinal lymph nodes will be conditioned by the location of the primary lesion.

We wish to report a case which is of particular interest from the standpoint of pathogenesis and the histological appearance of the lesions found in the mucous membrane and in the deeper layers of the oesophageal wall.

[1] From the Medical Service of the National Jewish Hospital, Dr. Charles J. Kaufman, Medical Director, Denver, Colorado.

S. G., a waiter, was first admitted to the National Jewish Hospital in 1915 at the age of thirty-three. The sputum was positive and a diagnosis of far advanced pulmonary tuberculosis was made. He was discharged at the end of eight months as improved. He returned to work and was fairly well until January, 1927, when he noted a marked increase in cough and expectoration. Pain in the throat, choking sensations and slight dyspnoea were also noted. Moderate abdominal pain, associated with belching, had been present since 1931. In May, 1937 he began to have severe attacks of pain in the right upper quadrant of the abdomen, radiating to the back, and this was associated with marked anorexia. Severe and persistent vomiting of coffee-ground material and the presence of tarry stools were also noted.

On readmission to this Hospital on June 4, 1937, at the age of fifty-six, the patient appeared dehydrated and emaciated. There was cyanosis of the lips and nail beds. Approximation of the vocal cords was poor, but the only visible lesion was a pale interarytenoid scar. The heart was not enlarged. There was a moderate tachycardia associated with slight pulse irregularity. The blood pressure was 124/82. Examination of the abdomen showed nothing abnormal. The urine contained a faint trace of albumin, occasional casts and a few red cells. The sputum was highly positive for tubercle bacilli on direct smear. There was a moderate anaemia and a white cell count of 12,700 with 72 per cent neutrophils. The sedimentation rate was 76 (Westergren). Kolmer and Kahn blood reactions were negative. Physical and X-ray examination of the chest revealed extensive fibrotic and cavitary changes in the left middle and upper lung fields, as well as some haziness of the right apex.

There were numerous episodes of haematemesis and chemical tests for blood in the stools were positive. The gall bladder could not be visualized by the administration of dye. Barium studies revealed deformity of the duodenal bulb as well as gastric residues after six and twenty-four hours. After a period of starvation, followed by milk and cream feedings, and finally a more liberal bland diet, the abdominal symptoms largely subsided and the haematemesis ceased.

In December, 1937, tachycardia (160), marked cardiac dilatation and oedema of the feet, legs, sacrum and face occurred. An electrocardiogram revealed an auricular origin of the tachycardia. Administration of digitalis, vitamin B and additional protein in the diet was followed by disappearance of the tachycardia, a considerable decrease in the transverse diameter of the heart and subsidence of the oedema. This episode was believed to be due in part at least to vitamin deficiency resulting from inadequate intake of food.

In August, 1937, patient began to complain of choking sensations and difficulty in swallowing. This grew progressively worse until even fluids were taken with difficulty. Excessive salivation and burning pain in the throat were also present. Examination of the larynx revealed tuberculomata and ulceration of the epiglottis of a degree insufficient to account for the dysphagia. Fluoroscopy and an X-ray film in February, 1938 revealed dilatation of the lower half of the oesophagus and a distinct narrowing in the region of the cardia. The oesophageal outline from the seventh to ninth dorsal vertebrae was irregular (figure 1).

Oesophagoscopy was performed. A fungating mass which bled easily was seen near the cardia. A biopsy was done, but no diagnosis of specific infection or of tumor could be made from the tissue removed. A moderate haemorrhage which followed this procedure stopped spontaneously.

The patient's clinical condition deteriorated rapidly and he died on May 20, 1938 after a period of high fever. A chest film taken two days before death suggested marked spread of the pulmonary tuberculosis.

FIG. 1

FIG. 2

FIG. 1. Roentgenogram of the barium filled oesophagus, demonstrating extreme narrowing of the lower third.

FIG. 2. Oesophagus and stomach opened posteriorly. Lungs and neck organs *in situ*. The haemorrhagic and congested area of the esophagus is located at A, the scarred and stenotic portion, adjacent to the cardia, at B.

Clinical diagnosis: Chronic pulmonary tuberculosis, far advanced; tuberculosis of the epiglottis; stenosis of oesophagus (origin unknown).

Autopsy revealed an extensive fibrosis and shrinking of the upper lobe of each lung. A small fresh cavity was present in the left upper lobe and an irregular caseous focus was found in the left apex. Both lower lobes were studded with acinous-nodose lesions and numerous confluent areas of bronchopneumonia were present. The mediastinal lymph nodes were slightly enlarged but failed to show tuberculous lesions. The heart was not enlarged. There was some slight

dilatation of the right auricle and a moderate amount of thickening of the valves. The coronary arteries showed no evidence of sclerosis and were patent throughout. There were several small yellowish areas in the tail of the pancreas, histological examination of which revealed necrosis but no specific tuberculous changes. The epiglottis was deformed and shrunken. Its internal surface showed a deep triangular defect, presenting the characteristics of a tuberculous ulcer.

There was marked dilatation of the upper half of the oesophagus. The wall of the lower third was thickened and the lumen narrowed, admitting only a small probe. Just above the cardia a dollar-sized area of the mucosa showed marked hyperaemia. In this area the folds of the mucosa were absent and only a few tiny polyps were visible. Above this hyperaemic area the mucosa was replaced by smooth white fibrous tissue. There was no gross evidence of ulceration or tubercle formation to suggest tuberculosis (figure 2).

Examination of the sections of the oesophagus taken from the hyperaemic area revealed cellular infiltration and hyperaemia of the mucous membrane. The submucosa and muscular layers contained several caseous and fibrotic nodules with numerous epithelioid and Langhans' giant cells. Acid-fast granules but no tubercle bacilli were found.

COMMENT

Although Lockard stated that subjective symptoms are in most instances lacking, the increasing frequency with which the condition has been diagnosed clinically in recent years suggests that this is not the case. The symptoms are not specific and consist of pain and difficulty in swallowing. When such complaints occur in a patient with chronic pulmonary, lymph node or spinal tuberculosis, one is justified in including tuberculosis of the oesophagus in the differential diagnosis. A few cases have been reported in which the onset has been very sudden. In ulcerative cases odynophagia is the chief symptom and is accompanied by spasmodic contraction. The absence of demonstrable stenosis does not rule out the disease.

Accurate diagnosis is made by means of biopsy carried out during oesophagoscopy. The prognosis appears to be grave in practically all cases. This is as much due to the associated systemic disease as to the local lesion. Treatment of this disease has not been efficacious. Gradual dilatation carried out in cases of stenosis may give some relief, and in ulcerative cases may reduce the spasm. Local treatment used in the past without success has included the electric cautery, topical application of lactic acid, orthoform and other types of medication. The exhibition of sedatives has an important rôle in keeping the patient comfortable.

The great difficulty in the analysis of this case was the determination of the pathogenesis of the tuberculous lesions of the oesophagus. The considerable distance of the lesion from the epiglottis, the absence of haematogenous foci and tuberculous lymph nodes, and the normal intestinal tract made direct extension, intracanalicular spread, and the haematogenous route improbable. The pres-

ence of tuberculous nodules in the muscular layers of the oesophagus points however towards a lympho-haematogenous origin of the lesions.

Clinical, oesophagoscopic and anatomical findings proved the presence of a narrowing of the lumen of the oesophagus just above the cardia. Hyperaemia of the mucous membrane and atrophy and fibrosis of the lower third of the organ were also present.

Even in the absence of historical data indicating a previous damage of the mucous membranes, such a possibility must be seriously considered as the basis for a subsequent tuberculous infection of the deeper layers of the oesophagus. Flexner's emphasis on the rôle of trauma (chemical, mechanical, tumor, etc.) of the mucous membrane as a predisposing factor in tuberculosis of the oesophagus should be kept in mind in the analysis of our case.

SUMMARY

A patient is described with chronic pulmonary tuberculosis and tuberculosis of the epiglottis who developed symptoms of oesophageal obstruction. Oesophagoscopic and biopsy findings were insufficient to permit a definite diagnosis. Autopsy revealed a haemorrhagic inflammation and fibrosis of the mucous membrane and fibrocaseous nodules in the muscular layer of the lower third of the oesophagus. Pathogenetically lymphogenic channels must be considered despite the absence of generalized tuberculosis and tuberculosis of lymph nodes in the mediastinum. Implantation of tubercle bacilli into a previously damaged mucous membrane cannot be excluded.

SUMARIO

Descríbese un caso de tuberculosis pulmonar crónica y de tuberculosis de la epiglotis que manifestó síntomas de obstrucción esofágica. Los hallazgos esofágicos y biópsicos no bastaron para permitir un diagnóstico bien definido. La autopsia reveló inflamación hemorrágica y fibrosis de la mucosa y nódulos fibrocaseosos en la capa muscular del tercio inferior del esófago. Hay que considerar patogénicamente las vías linfógenas a pesar de la falta de tuberculosis generalizada y de tuberculosis de los ganglios linfáticos del mediastino. Tampoco puede excluirse el implante de bacilos tuberculosos en una mucosa previamente lesionada.

REFERENCES

(1) Flexner, S.: Bull. Johns Hopkins Hosp. 1893, *4*, 4.
(2) Lockard, L.: Laryngoscope, 1913, *23*, 561.

EDITORIAL

The Patient with Occasionally Positive Sputum following Apparently Adequate Treatment

In the contributions to the symposium on this topic, held at the last annual meeting of the American Trudeau Society (published in this issue of the REVIEW), quite a number of sound and important suggestions were made. The clinician has justly stressed the importance of special diagnostic methods in attempts to determine the source of the bacilli and the necessity of recognizing that certain patients in this group cannot and should not be subjected to further treatment. The pathologist has shown what type of lesions may give rise to occasionally positive sputum. The nurse has stressed what she can do in diagnosis, treatment and information. The public health worker has most wisely emphasized that patients with positive sputum, particularly with paucibacillary sputum, are not the menace that myopic opinion has so often stamped them to be, especially if they are successfully educated.

All these points have lent emphasis to practices and opinions that are, more or less, common knowledge, at least in centres of tuberculosis work. But even a benign appraisal of this symposium must conclude that the problem has been stated in its various aspects, but that no new knowledge for its solution has been added.

It has been well to reëmphasize that the technique of sputum examination determines to a large extent how many patients fall into this problematical group. However, the crux of the matter is likely to lie even deeper. Not only has every technical improvement in bacteriological work detected tubercle bacilli in more and more patients, but it has been shown that a simple repetition of the same examination produces more positive findings. It can hardly be questioned that many more patients on discharge have actually "occasionally positive" sputum (or gastric contents) than are so recorded.

One of the fundamental aspects of the problem is the question whether patients with arrested pulmonary tuberculosis (according to Diagnostic Standards which require only concentration tests) and who never had any positive sputum or gastric cultures during their last six months of hospitalization have a better prognosis than patients who meet the same diagnostic requirements, but who had one or two positive cultures during their last half year of hospitalization. An answer to this question is not available at present. Only a significant prognostic difference would justify further treatment of the second group of patients. Specific problems arise continuously: should an apparently satisfactory pneumothorax be abandoned, say after one or two years' duration, exclusively on the indication of a few positive cultures? Should thoracoplasty be advised in such a patient? Is the risk of revision operations or other surgical procedures justified for these reasons?

Particularly when patients are considered who had apparently adequate

collapse therapy, is there any justification for the assumption that those with occasionally positive cultures are *really* different from those whose bacteriological findings are always negative? Or may it not be that in many or all of the negative group occasional tubercle bacilli are present but are not detected? Posing these questions is no indication of the writer's answer; he has none. It is obviously of the greatest importance to collect factual material by a sufficiently long follow-up of the two groups of patients. Only objective data based on actual observation will help solve the problem. At the present time, many patients are rehospitalized and treated on the sole indication of an occasionally positive sputum. Is this a justified indication in patients who have already had what appeared to be adequate treatment?

It would seem likely that quite a few tuberculosis hospitals have complete records of a sufficient number of patients to contribute important data. It is the sole purpose of these lines to encourage the collection and publication of pertinent observations.

MAX PINNER

American Trudeau Society

Report of the Committee on Tuberculosis Sanatorium Standards

Dr. Fred H. Heise, *Chairman*

Dr. John F. Busch	Dr. John Nicklas
Dr. Ralph Horton	Dr. John W. Towey
Dr. Victor F. Cullen	Dr. Buford H. Wardrip

The members of the Committee on Tuberculosis Sanatorium Standards of the American Trudeau Society met at the Hotel Pennsylvania in New York City, October 30, 1941.

Preliminary to the discussion of the Standards, Mr. J. B. Basil, architect, presented tuberculosis clinic and sanatorium planning analyses in which he emphasized the physical construction on a basis of ease of motion for those engaged in the various duties of the institution and the accessibility of the different departments.

Dr. H. A. Pattison asked that the Committee on Tuberculosis Sanatorium Standards approve a set of record forms so that such forms, printed by the Potts Memorial Hospital, would bear the sanction of the Committee.

After the formal opening of the Committee meeting, the feasibility of attempting to apply tuberculosis sanatorium standards to the different parts of the country was discussed, as well as the various fields to be covered in the work of this Committee. It was thought that the Executive Committee of the American Trudeau Society should be approached with the idea of having the extent of the Committee's work outlined and a decision reached as to whether or not its work should include such items as the standards for physical properties, administration, personnel, diagnostic and laboratory standards, etc. The medical standards were discussed and a revised report of these standards set up. In addition to the revised Standards, the Committee has received considerable data as to salaries and personnel in the various sanatoria. As yet these have not been tabulated.

The Committee has been informed by the Executive Committee that for the present at least it should limit its work to the medical and administrative standards. Other suggestions from the Executive Committee included the desirability of describing separately the functions of the Superintendent and Medical Director, and that a tentative report be submitted to the various sanatoria for comment.

All of the above transpired before December 7. Since then the United States has gone to war and the Committee, after consideration, thinks it advisable not to present any standards for consideration or adoption at the present time for the following reasons: first, because the medical and nursing personnel of the sanatoria are being severely drawn upon due to the war needs; second, because during and after the war there perhaps will be additional difficulty in obtaining funds for the proper running of the sanatoria.

The Committee, however, felt that the Tuberculosis Sanatorium Standards Committee should be continued and that its work should be carried on so that at the expiration of the war it would be ready to submit proper standards which would be in conformity with the facts of the situation at that time. Also, it would act in an advisory capacity to any who would care to apply for advice. It was thought that at least one meeting of the Committee in the coming fiscal year would be desirable.

American Trudeau Society

Report of the Committee on Rehabilitation

Dr. P. P. McCain, *Chairman*
Dr. H. F. Carman Dr. B. S. Pollak

The Committee is gratified at the increasing interest that is being manifested in the rehabiliatation both of tuberculous patients themselves and also of their families. We especially commend the example of those institutions which have established well rounded rehabilitation programs with trained social workers and occupational therapists. A beginning is made with patients as soon as their physicians say they are well enough to be consulted and tested concerning their tastes and aptitudes to determine what occupations are suitable for them. The patients are followed until their training is finished and they are assisted in finding suitable positions. The resumption of active and useful postsanatorium lives despite certain physical limitations is held out to them as an encouragement to full coöperation in their treatment.

We recommend that all physicians and other staff members of sanatoria which cannot finance a well rounded rehabilitation program call upon all volunteer and official agencies which might render aid in the rehabilitation of their patients who are able to take training, both while they are patients in the institution and after their discharge. The State and local tuberculosis associations may be able to furnish funds, equipment and workers. The Rehabilitation Department of the National Tuberculosis Association will be glad to advise and assist in any way possible. State and local welfare agencies are often interested and helpful. State Rehabilitation Departments are most coöperative. They are willing to furnish equipment and tuition to all tuberculous patients whose disease is under control and whose sputum has been negative for six months or more in some occupation which they can safely follow. They can also furnish board and treatment for a limited number. We feel, of course, that patients whose previous occupations constitute no hazard should return to their previous positions.

There is at present before Congress House Bill HR-5906, which provides for the appropriation of an additional $5,000,000 to be made available to the Vocational Rehabilitation Departments of the various States in proportion to their population. We recommend that all those interested in rehabilitation write to their Congressmen and Senators and ask them to support this bill.

We feel that there is special need for the rehabilitation of tuberculous Negro patients. Most of them are laborers and cannot go back to their former work without a great risk of reactivating their disease. Their education is limited and there are few occupations which they can safely follow. We trust that rehabilitation workers will give this phase of the problem their special attention.

In certain sections there is still considerable prejudice against the reëmployment of arrested tuberculous patients. This problem is all the more complicated in States in which tuberculosis is a compensable disease. We urge that all physicians and tuberculosis associations do all in their power to overcome this prejudice.

Medical Library DEC 15 1942

INDEX NUMBER
THIS NUMBER COMPLETES VOLUME XLVI

Vol. XLVI DECEMBER, 1942 No. 6

THE AMERICAN REVIEW OF TUBERCULOSIS

OFFICIAL JOURNAL
AMERICAN TRUDEAU SOCIETY

EDITOR
MAX PINNER, New York, N. Y.

EDITORIAL BOARD

JOHN ALEXANDER, Ann Arbor, Mich.
J. BURNS AMBERSON, JR., New York, N. Y.
E. R. BALDWIN, Saranac Lake, N. Y.
H. J. CORPER, Denver, Col.
F. S. DOLLEY, Los Angeles, Calif.
BRUCE H. DOUGLAS, Detroit, Mich.
L. U. GARDNER, Saranac Lake, N. Y.
ROSS GOLDEN, New York, N. Y.
ESMOND R. LONG, Philadelphia, Pa.
LEWIS J. MOORMAN, Oklahoma City, Okla.
D. W. RICHARDS, JR., New York, N. Y.

PUBLISHED MONTHLY
at Mount Royal and Guilford Avenues, Baltimore, Md.
by the
National Tuberculosis Association
Business Office, 1790 Broadway, New York, N. Y.

Copyright 1942, by the National Tuberculosis Association

CONTENTS

ROSENBLATT, MILTON B., FULLAM, ERNEST F., AND GESSLER, ALBERT E. Studies of Mycobacteria with the Electron Microscope 587

GERSTT, BRUNO, AND TENNANT, ROBERT. Enzymes as Factors in Resistance to Tuberculosis 600

GUNN, F. D., SHEEHY, J. J., COLWELL, CHARLOTTE A., AND MILLS, M. A. Experimental Pulmonary Tuberculosis in the Dog. BCG Immunization 612

FLOYD, C., NOVACK, H. A., AND PAGE, C. G. Gastric Lavage in Healthy Adolescents. A Bacteriological Study of Fasting Gastric Contents for Tubercle Bacilli 622

FRANCO, S. E., AND GUREVITCH, J. Atypical Findings on Animal Inoculation 625

MORRISS, W. H. Pneumothorax Treatment. Subsequent History of Tuberculous Patients after their Selection for Pneumothorax 628

TICE, FREDERICK. Ambulatory Pneumothorax. Results of Ten Years' Experience 639

GEARY, PAUL. Extrapleural Pneumothorax. Late Results 646

HASTINGS, D. R., AND BEHN, BORGHILD. Pneumothorax Cases Treated at a Clinic 656

PANEL DISCUSSION:

ALEXANDER, JOHN. Postoperative Pulmonary Complications. From the Point of View of the Surgeon 664

RIGGINS, H. McLEOD. Postoperative Pulmonary Complications. From the Point of View of the Internist 666

PINNER, MAX. Treatment of Postoperative Pulmonary Complications. From the Point of View of the Pathologist 674

CLERF, LOUIS H. Treatment of Postoperative Pulmonary Complications. From the Point of View of the Bronchoscopist 675

MANNING, ALICE LOVE. Treatment of Postoperative Pulmonary Complications. From the Point of View of the Nurse 676

McDOUGALL, J. B. Tuberculosis in England during the War 677

VOORHANGER, WILLIAM C. Arytenoid Extrusion with Roentgenological Studies 684

PETERSEN, WILLIAM F. Browning's Meteoropathological Observations in Tuberculosis 690

STATISTICAL DATA 697

AMERICAN TRUDEAU SOCIETY

Report of the Committee on Educational Literature 701

Index of Subjects and Authors 707

Index of Abstracts 83

S.S.V.T.

Strasco Special Vitamin Tablets

D.D.V.T.

The revised formula of Strasco Special Vitamin Tablets necessitating only one tablet per day, furnishes the daily minimum requirement of vitamins A B D G as recommended by the National Nutrition Council.

Due to the fact that the Vitamin A in the tablet is obtained by special High Vacuum Molecular Distillation, which removes the undesirable parts of the origin-

NEW FORMULA

Vit. A - 5,000 U.S.P. Units
(In natural ester form)
Vit. D - 500 U. S. P. Units
Vit. B_1 - 330 Int. Units
(1 mg. Thiamine Hydrochloride)
Vit. B_2 - 2000 micrograms
(2 mgs.)

al fish liver oils, no regurgitation follows the administration of Strasco Special Vitamin Tablets.

This tablet has been designed as a dietary aid for the prevention of "cold infections".

Supplied in bottles of 100, 500 and 1000.
R. J. Strasenburgh Company, Pharmaceutical Chemists Since 1886, Rochester, N. Y.

Entered as second-class matter March 9, 1917, at the postoffice at Baltimore, Md., under the Act of August 24, 1912. Acceptance for mailing at special rate of postage provided for in Section 1103, act of October 3, 1917. Authorized on July 2, 1918.

STUDIES OF MYCOBACTERIA WITH THE ELECTRON MICROSCOPE[1]

MILTON B. ROSENBLATT, ERNEST F. FULLAM AND ALBERT E. GESSLER

Although the science of optics dates back more than two thousand years, the first practical microscope for scientific observation was described by Leeuwenhock in 1673 (1). In the years which followed, numerous improvements were made to increase the usefulness of the instrument. However, it was eventually realized that there was a limitation to the use of light as a means of observation. Although the image could be greatly magnified, the microscope's resolving power, or the ability to discriminate between minute adjacent objects, was not increased proportionately.

Objects which are markedly smaller than half the wave-length of light cannot be observed with the optical microscope. The wave-length of light in the visible range is from .000,4 to .000,7 mm. and objects less than .000,2 mm. are indistinct or invisible (2, 3). Inasmuch as many of the structural components of bacteria are smaller than this, it has been impossible to study them with the optical microscope.

The observation that the path of electrons in a magnetic field was similar to that of light in relation to lenses led to the development of the electron microscope (4, 5, 6, 7, 8, 9). Many attempts were made to produce a practical instrument in this country, but it was not until 1940 that this was accomplished by Zworykin and his associates at the R. C. A. Laboratories (plate 1, figure A).

The electron microscope allows for full resolution of an object at magnifications up to 100,000. This is due to the minute wave-length of the electron beam. At a velocity of 60 kilovolts it is one-hundred thousandth that of light. Therefore, objects which are far smaller than the wave-length of light may readily be observed with this new instrument. There have already been reported studies on the structure of bacteria (2, 6, 10, 11) and on viruses (12, 13, 16). The present investigation was undertaken to study the structural composition of various types of mycobacteria.

TECHNIQUE

The technique employed with the electron microscope is entirely different from that with the light microscope. Since electrons will be dissipated in contact with air the entire path of the electron beam must be maintained at a vacuum of at least 0.1 μ of mercury.

The electrons are emitted from a heated tungsten filament and accelerated downward through the instrument in the form of a beam which is deflected by the magnetic lenses. The first stage of magnification produces an image of approximately 100 diameters. Near the lower end of the instrument a small portion of this shadow is further enlarged. The final shadow of the object is

[1] From the Division of Pulmonary Diseases, Montefiore Hospital for Chronic Diseases, and the Research Laboratories of the Interchemical Corporation, New York.

formed on a fluorescent screen at a magnification up to 24,000 diameters. The fluorescent screen is adjusted so that it may be replaced by a photographic plate for permanent recording and for subsequent enlargement.

There are two important steps in the study of acid-fast bacilli with the electron microscope. The first is the preparation of a suspension of sufficient uniform density to permit rapid visualization of the organisms. This is obtained by carefully grinding in a mortar small portions of a pure culture to which is added physiological saline drop by drop. Distilled water may be used instead of saline if the material is to be studied shortly after preparation. The proper concentration of bacteria in suspension was determined with the spectrophotometer to be one that gave a transmittance of 81 per cent at 540 millimicra when contained in a one centimeter glass cell.

The second step is the mounting of the specimen. A film of nitrocellulose (collodion) of about 0.000,01 mm. is formed by placing one drop of a 2 per cent solution of highly purified nitrocellulose in amyl acetate on distilled water in a wide dish. As the drop spreads the solvent evaporates and a membrane results which will readily transmit most of the electrons. A small portion of this film is picked up on a chromium screen 3 mm. in diameter which is composed of a fine meshwork (57,600 holes per square inch). The screen is then placed on a metal plug with the film on top. The excess water is drawn off and the film is dried thoroughly.

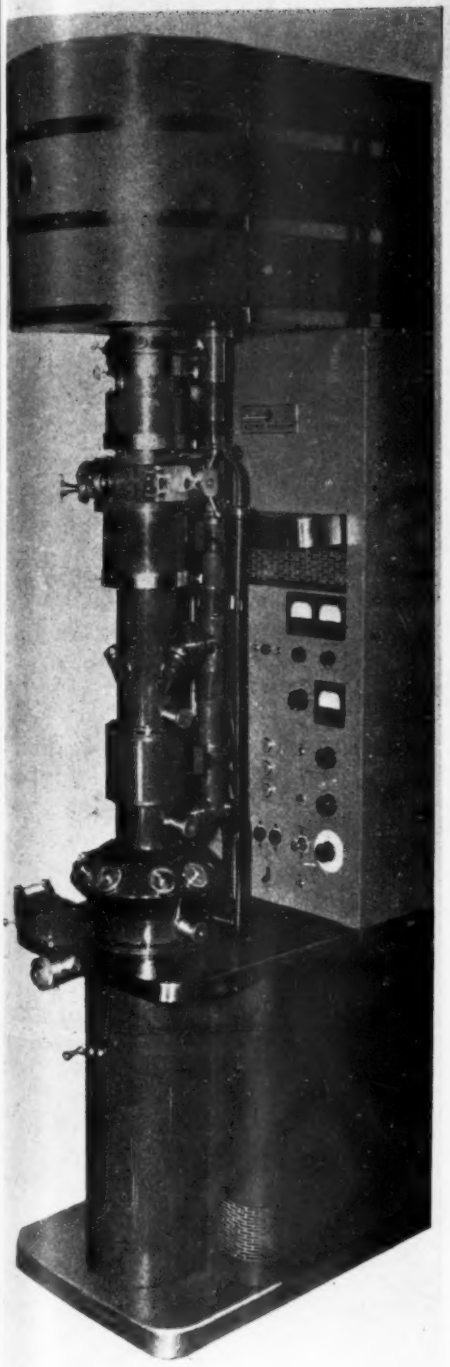
Using a capillary pipette a small drop of the bacillary suspension is placed on the film and permitted to dry. If the suspension was properly prepared the bacilli will be evenly distributed over the film. The screen is then turned over and placed in a brass capsule which is inserted in the microscope through a system of air locks. The organisms are now ready for viewing on the fluorescent screen (plate 1, figures B, C and D).

If saline is used in the bacterial suspension it may crystallize and the crystals may obstruct the view of the bacteria. This may be corrected by dialysis. A drop of concentrated suspension is placed on a nitrocellulose film on top of distilled water. After three to four hours the saline will have diffused through the membrane into the distilled water and the water will have diffused into the saline suspension. A screen is placed on the enlarged drop and the excess liquid is withdrawn with a pipette. The screen is then picked up with the film, dried and placed in the microscope as described above.

RESULTS

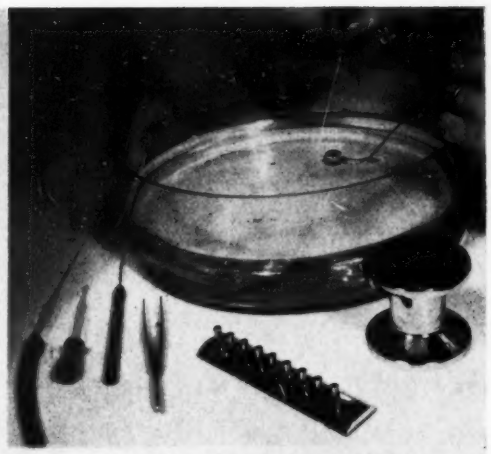
Before describing our findings we should first like to express our indebtedness to Dr. Max Pinner of Montefiore Hospital, Dr. M. Maxim Steinbach of Columbia University and Mr. W. Steenken, Jr. of Trudeau Sanatorium for their kindness in furnishing us with the bacterial cultures.

The electron microphotographs shown were selected because they are typical specimens of the organisms under investigation. During the course of the study many variations in size, shape and internal structure were encountered. These are discussed separately in the legends.

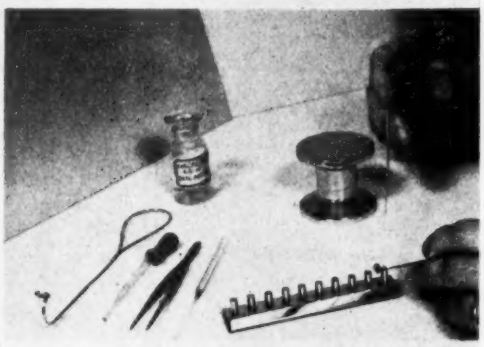


THE ELECTRON MICROSCOPE

A



B THE SCREEN IS REMOVED FROM THE COLLODION FILM



A DROP OF BACTERIAL SUSPENSION IS PLACED ON THE SCREEN C

D THE SCREEN IS INSERTED IN THE BRASS CAPSULE

DISCUSSION

I. Mycobacterium Tuberculosis Hominis

The morphological characteristics of the human tubercle bacillus have been described from observations with the optical microscope (14, 15). Studies with the electron microscope confirm many of these observations and also yield additional information, particularly in regard to internal structure.

Size: The electron photographs show that the bacillus varies in length from 0.8 to 5.5 μ and in width from 0.2 to 0.6 μ. There are numerous variations in size among bacilli from different cultures and even from the same culture. The bacilli in figures 1 and 2 measure 1.5 x 0.6 μ but other bacilli from this culture were as small as 0.8 x 0.4 μ. The bacilli in figures 3 and 4 measure 1.5 x 0.5 and 1.8 x 0.4 μ, respectively, while other bacilli from the culture were 1.0 x 0.3 μ. Figures 5 and 9 show bacilli from different cultures of the H37 strain. The organisms subcultured at Columbia University varied in size from 4.3 x 0.4 μ (figure 5) to 1.0 x 0.2 μ. The cultures from Trudeau showed the largest size to be 1.8 x 0.6 μ (figure 9) and the smallest 1.0 x 0.3 μ. The H4 RA strain also showed differences in size. The bacilli in figures 6 and 7 measure 2.5 x 0.5 and 2.0 x 0.5 μ, respectively, but other bacilli from this culture measured 1.4 x 0.3 μ.

Shape: The predominant form of the bacillus is rod shaped with rounded or slightly flattened ends. However, curved, bean-shaped and oval forms are common. Many of the bacilli appear distorted but this may be a result of the technique used in the preparation of the specimen. Branching, which has been described from studies with the optical microscope, was not observed.

Capsule: The presence of a membrane, or capsule surrounding the tubercle bacillus has been generally questioned. The electron photographs, however apparently show that a membrane is uniformly present. In some bacilli it is relatively thick and measures 0.03 μ (figures 1 and 2). In many instances the membrane contains granules.

Internal structure: The tubercle bacillus apparently consists of one or more dense nuclear masses within a granular cytoplasm. Further studies will be necessary to confirm the precise nature of these structures but for the present they will be described as nucleus and cytoplasm. The nuclear masses vary considerably in size and in density often appearing granular. They are generally found at the ends of the bacillus. When there are many nuclear bodies they are usually distributed throughout the long axis. There are often spaces between the nuclei which give the bacillus a beaded effect.

The irregularities in distribution of the nuclear material probably account for the variations observed in the stained specimens. The stained bacillus will appear clubbed if the nuclei are at the periphery and beaded if the nuclei are arranged at intervals in the long axis.

The cytoplasm varies considerably in density and usually contains many granules. Large and small vacuoles are frequently present.

II. Acid-fast Chromogenic Bacilli

These organisms were described in some detail by Pinner (17). The colonies are yellow or orange in color with smooth surfaces and have a creamy consistency. They were isolated from human sputum, urine or secretions.

The electron photographs show no outstanding differences between the human tubercle bacilli and the chromogenic bacilli in regard to shape, membrane or internal structure. There appears to be, however, a difference in size. The majority of the chromogenic bacilli are longer and thinner than the tubercle bacilli. Chromogenic bacilli measuring more than 5 μ in length and only 0.3 μ in width were found frequently.

III. Pathogenic and Nonpathogenic Acid-fast Bacilli

(a) *Mycobacterium tuberculosis bovis:* Most of the bovine tubercle bacilli observed were short and plump, averaging about 1.0 μ in length and 0.5 μ in width. However, longer and thinner forms were also found. The bacillus in figure 15 is bean-shaped and that in figure 16 is ovoid but rod-shaped forms were present in equal numbers. A surrounding membrane was uniformly present. The nuclear material was arranged in dense masses or granules and was usually distributed throughout the long axis. In some instances the cytoplasm appeared homogeneous and in others it was granular.

(b) *Mycobacterium tuberculosis avium:* The bacilli from this culture were usually rod-shaped and averaged about 1.0 μ in length and 0.3 μ in width (figure 17). There were occasionally found much longer bacilli, one of which measured 6.0 x 0.7 μ. A surrounding membrane was present which often contained granules. The nuclear material was either confined to the periphery or distributed throughout the long axis of the bacillus. The cytoplasm appeared granular.

(c) *Mycobacterium phlei (timothy hay bacillus):* This saprophytic acid-fast bacillus closely resembles the pathogenic forms. The bacillus shown in figure 18 measures 1.1 x 0.4 μ. It is rod-shaped and has rounded ends. There are several large round nuclear masses arranged in the long axis. Large and small granules are present in the cytoplasm and in the surrounding membrane. Most of the bacilli from this culture were of approximately equal size and shape. The variations occurred chiefly in the arrangement of the nuclear material which was occasionally restricted to the ends or distributed throughout the cytoplasm in the form of dense granules.

(d) *Mycobacterium leprae (Duval strain):* The resemblance between these bacilli and the tubercle bacilli is very marked. The bacilli shown in figure 19 range in length from 1.4 to 1.8 μ and in width from 0.5 to 0.7 μ. They are rod-shaped with rounded ends. The surrounding membrane is very prominent. The nuclei are round and are distributed throughout the bacillus. The cytoplasm is dense and homogeneous. The bacillus in figure 20 is somewhat longer and slightly curved. Its nuclear material is arranged in the form of large and small granules.

(e) *Mycobacterium marinum:* These bacilli are in the majority of instances far longer than the human, bovine and avian forms. The bacillus in figure 21 measures 3.7 x 0.5 μ and other bacilli are greater than 5.0 μ in length. The predominant form is a long thin rod with rounded ends and a surrounding membrane. Numerous small and large nuclei are distributed throughout. The cytoplasm is fairly dense and granular and contains hexagonal structures resembling vacuoles.

(f) *Mycobacterium smegmatis:* This saprophyte closely resembles the tubercle bacilli in size, shape and internal structure. The bacilli range in length from 1.5 to 3.0 μ. The bacillus in figure 22 measures 3.0 x 0.5 μ. The variations in width are probably due to distortion as other bacilli from this culture are of uniform width. The predominant form is rod-shaped with rounded ends but curved forms are frequently found. Figure 22 shows a prominent surrounding membrane partially elevated at the upper end. Several large nuclear masses are distributed throughout a fairly dense cytoplasm.

REFERENCES

(1) HADEN, R. L.: Early microscopes and early microscopists, Tr. A. Am. Physicians, 1939, *54*, 343.

(2) BURTON, E. F., HILLIER, J., AND PREBUS, A.: The contribution of the electron microscope to medicine, Canad. M. A. J., 1940, *42*, 116.

(3) DAVIS, W.: Exploring a new world, Science News Letter, 1940, *38*, 227.

(4) RUSKA, E.: Über Fortschritte im Bau und in der Leistung des magnetischen Elektronemikroscops, Z. Physik, 1934, *87*, 580.

(5) MARTON, L.: La Microscopie Electronique des Objets Biologique, Bull. Acad. roy. de Méd. de Belgique, 1934, *20*, 439.

(6) MARTON, L.: The electron microscope, J. Bact., 1941, *41*, 397.

(7) ZWORYKIN, V. K.: An electron microscope for the research laboratory, Science, 1940, *92*, 51.

(8) SCOTT, G. H.: The electron microscope, Washington Univ. Med. Alumni Quart., 1941, *4*, 165.

(9) PREBUS, A., AND HILLIER, J.: The construction of a magnetic electron microscope of high resolving power, Canad. J. Research, 1939, *17* (Section A.): 49.

(10) MUDD, S., AND LACKMAN, O. B.: Bacterial morphology as shown by the electron microscope, J. Bact., 1941, *41*, 415.

(11) MUDD, S., POLEVITZKY, K., ANDERSON, T. F., AND CHAMBERS, L. A.: Bacterial morphology as shown by the electron microscope, Ibid., 1941, *42*, 251.

(12) ANDERSON, T. F., AND STANLEY, W. M.: A study by means of the electron microscope of the reaction between tobacco mosaic virus and its antiserum.

(13) STANLEY, W. M., AND ANDERSON, T. F.: A study of purified viruses with the electron microscope, J. Biol. Chem., 1941, *139*, 325.

(14) BERGEY, D. H.: Manual of Determinative Bacteriology, 4th ed., Williams & Wilkins Co., Baltimore, 1934, pp. 536–544.

(15) GAY, F. P.: Agents of Disease and Host Resistance, Charles C. Thomas, Springfield, Illinois, 1935, pp. 968–970.

(16) LEVADITI, C., AND BONÉT-MAURY: Les ultravirus considérés à travers le microscope electronique, Presse méd., 1942, *17*, 203.

(17) PINNER, M.: Atypical acid-fast microörganisms, Am. Rev. Tuberc., 1935, *32*, 424.

PLATES

PLATE II

Mycobacterium Tuberculosis Hominis (virulent forms)

FIGS. 1 and 2. Tubercle bacilli isolated by Doctor Trudeau in 1891 and dissociated by Mr. Steenken into Rl RA (1). Subcultured on March 31, 1942 and photographed on May 25, 1942. Magnification: 30,000 diameters. The bacilli measure 1.5 x 0.6 μ.

FIGS. 3 and 4. Tubercle bacilli isolated from the sputum of a patient at Montefiore Hospital. Cultured on February 24, 1942 and photographed on May 21, 1942. Magnification: 30,000 diameters. The bacillus in figure 3 measures 1.5 x 0.5 μ and that in figure 4 measures 1.8 x 0.4 μ.

FIG. 5. H37 strain subcultured by Doctor Steinbach at Columbia University on February 26, 1942 and photographed on May 7, 1942. Magnification: 30,000 diameters. Measures 4.3 x 0.4 μ.

FIGS. 6 and 7. H4 RA strain isolated from the sputum of a patient at Trudeau in 1937. Subcultured on March 31, 1942 and photographed on May 25, 1942. Magnification: 30,000 diameters. The bacillus in figure 6 measures 2.5 x 0.5μ and that in figure 7 measures 2.0 x 0.5 μ.

FIG. 8. Tubercle bacillus cultured from the sputum of a patient at Montefiore Hospital on February 27, 1942 and photographed on March 24, 1942. Magnification: 17,800 diameters. Measures 1.1 x 0.3 μ.

FIG. 9. Strain H37 RA isolated by Doctor Baldwin in 1905 and dissociated by Steenken, Oatway and Petroff in 1934. Subcultured by Mr. Steenken on March 31, 1942 and photographed on May 25, 1942. Magnification: 30,000 diameters. Measures 1.8 x 0.6 μ.

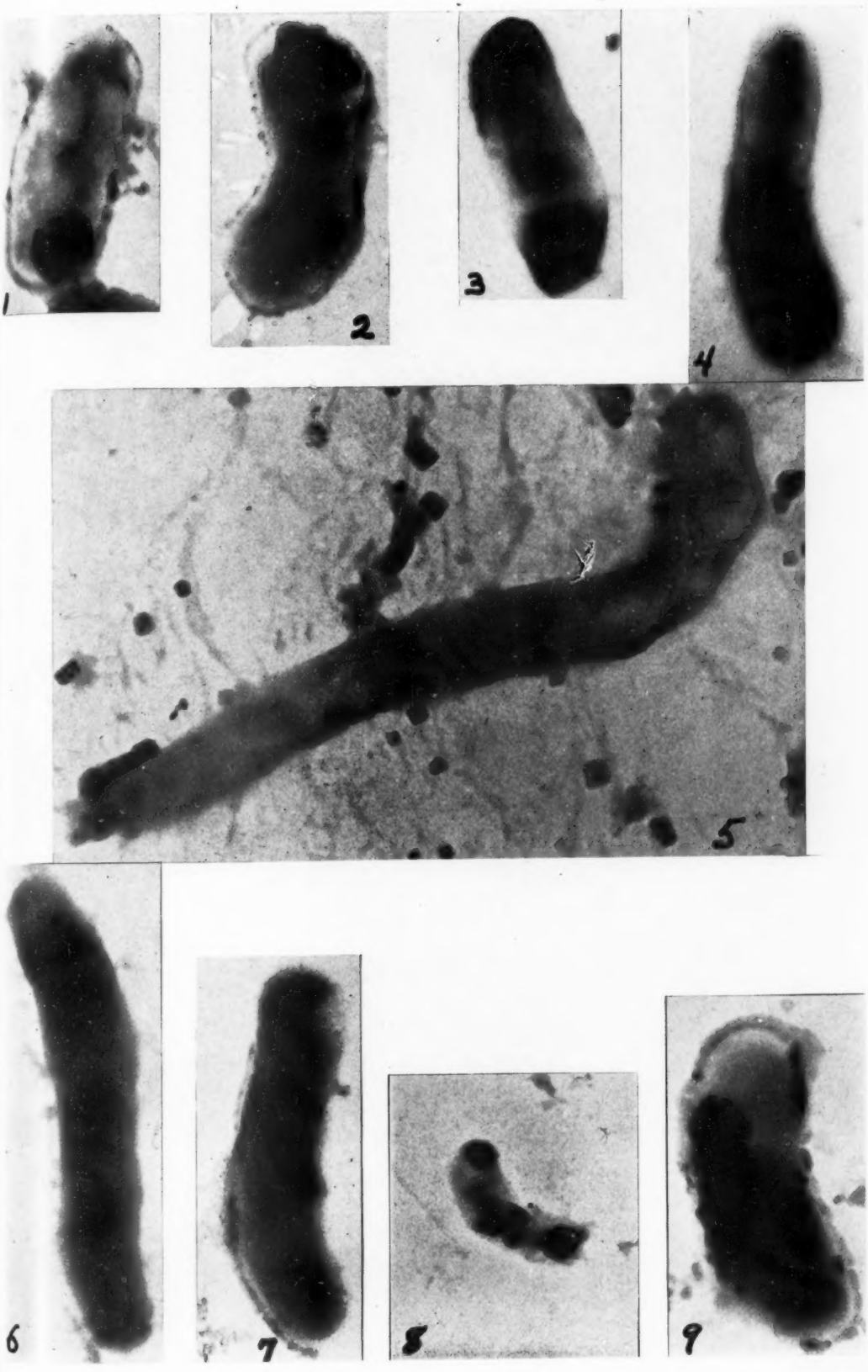


PLATE II

Plate III

Acid-fast Chromogenic Bacilli

Isolated from the sputum of a patient at Montefiore Sanatorium by Doctor Pinner. Subcultured on January 22, 1942 and photographed on May 21, 1942.

Fig. 10. Magnification: 20,500 diameters. Photograph shows two isolated bacilli and a small cluster below. The bacillus on the left measures 0.8 x 0.4 μ and that on the right measures 1.0 x 0.5 μ.

Fig. 11. Magnification: 30,000 diameters. Both bacilli are approximately equal in size and measure 1.6 x 0.4 μ.

Fig. 12. Magnification: 12,700 diameters. The upper bacillus measures 3.8 x 0.6 μ and the lower measures 2.0 x 0.6 μ.

Fig. 13. Magnification: 30,000 diameters. Measures 3.4 x 0.5 μ.

Fig. 14. Magnification: 30,000 diameters. The plump bacillus measures 1.0 x 0.5 μ. The long thin bacillus measures 5.5 x 0.3 μ. It appears to be twisted.

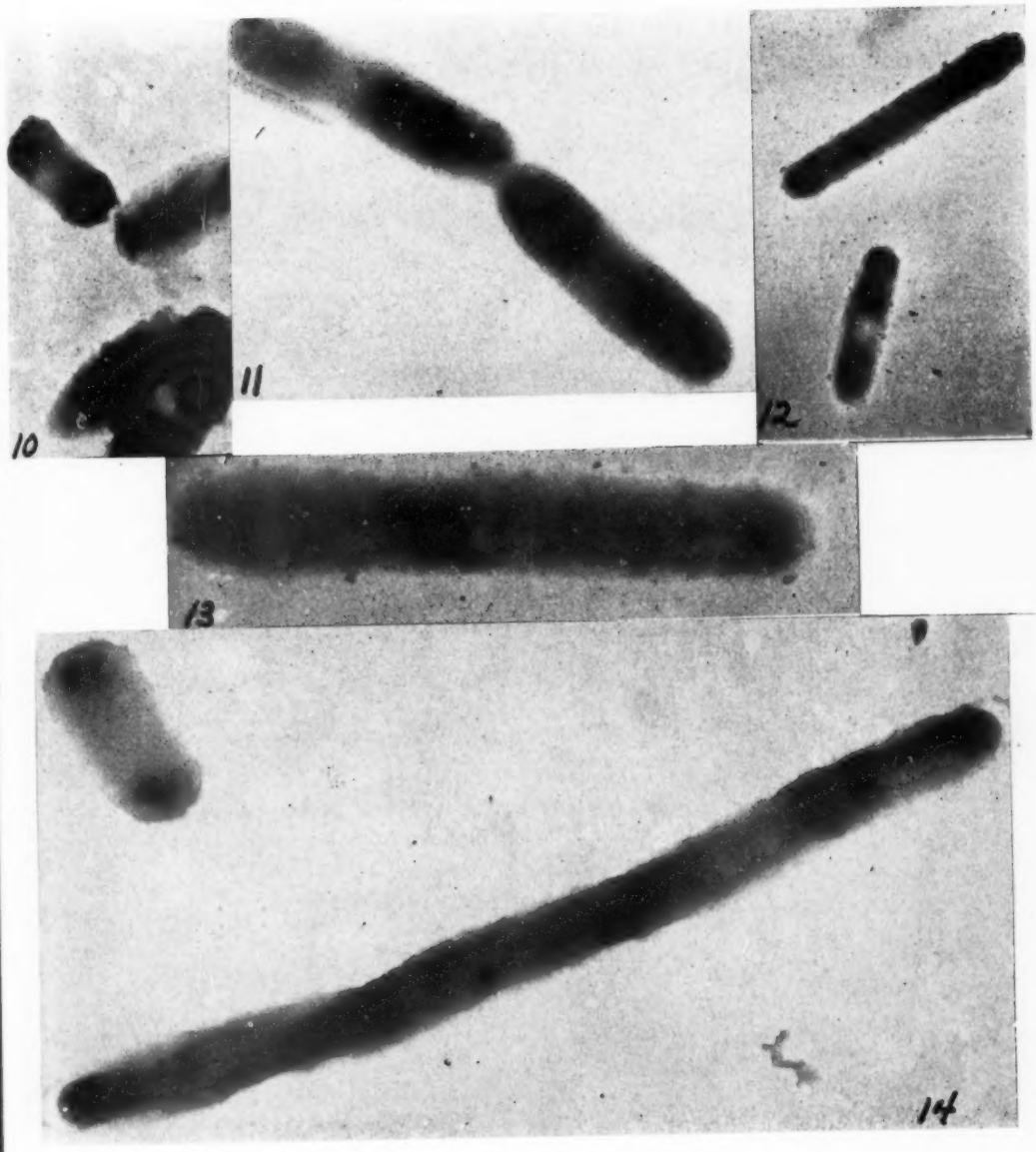


PLATE III

Plate IV

Pathogenic and Nonpathogenic Acid-fast Bacilli

Figs. 15 and 16. *Mycobacterium tuberculosis bovis:* Subcultured by Doctor Steinbach on February 24, 1942 and photographed on April 30, 1942. Magnification: 30,000 diameters. The bean shaped bacillus in figure 15 measures 1.2 x 0.5 μ. The ovoid bacillus in figure 16 measures 1.0 x 0.5 μ.

Fig. 17. *Mycobacterium tuberculosis avium:* Subcultured by Doctor Steinbach on February 17, 1942 and photographed on April 30, 1942. Magnification: 20,500 diameters. Measures 1.0 x 0.3 μ.

Fig. 18. *Mycobacterium phlei* (*timothy hay bacillus*)*:* Subcultured by Doctor Steinbach on October 14, 1941 and photographed on April 30, 1942. Magnification: 30,000 diameters. Measures 1.1 x 0.4 μ.

Figs. 19 and 20. *Mycobacterium leprae* (*Duval strain*)*:* Subcultured by Doctor Steinbach on February 18, 1942 and photographed on May 7, 1942. Magnification: 30,000 diameters. Figure 19 shows three bacilli two of which appear joined. They range in length from 1.4 to 1.8 μ and in width from 0.5 to 0.7 μ. Figure 20 shows another lepra bacillus which measures 1.8 x 0.6 μ.

Fig. 21. *Mycobacterium marinum:* Subcultured by Doctor Steinbach on December 23, 1941 and photographed on May 14, 1942. Magnification: 30,000 diameters. Measures 3.7 x 0.5 μ.

Fig. 22. *Mycobacterium smegmatis:* Subcultured by Doctor Steinbach on February 18, 1942 and photographed on May 14, 1942. Magnification: 20,500 diameters. Measures 3.0 x 0.5 μ.

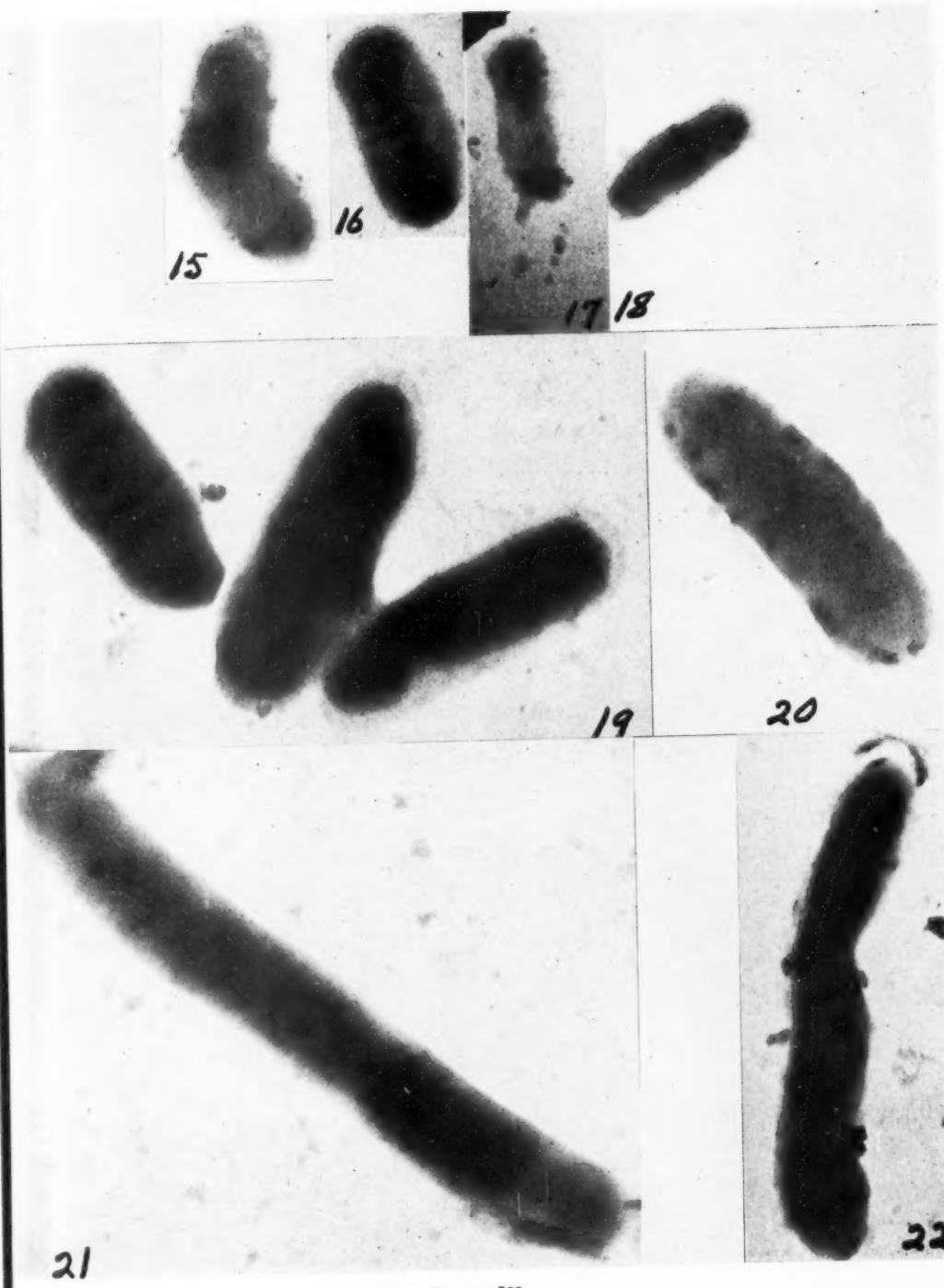


PLATE IV

ENZYMES AS FACTORS IN RESISTANCE TO TUBERCULOSIS[1, 2, 3]

BRUNO GERSTL AND ROBERT TENNANT

The mechanisms underlying the variations in the tissue response and in the progress of tuberculous infection among various species have interested numerous investigators. Lurie (1) has demonstrated different disease types in experimental tuberculosis of the rabbit. These, he believes, depend upon variations in inherited resistance and provide the analogy for explanation of differences manifested by different human ethnic groups. A number of constitutional factors has been suggested to explain these differences (Long (2)). Among these, the importance of cellular activity of the mononuclear phagocyte was suggested by the studies of Sabin and her coworkers (3) and further emphasized by the recent investigations of Lurie (4).

Enzymes are largely responsible for chemical processes accomplished within the cell. These studies are concerned with the rôle cellular enzymes may play in the interaction between host and invading tubercle bacillus.

It may be recalled that the tubercle phosphatide (5) is the constituent of the tubercle bacillus responsible for tubercle formation (Sabin, *l.c.*). It was shown that the breakdown of the tubercle phosphatide can be accomplished by enzymes (6) and that two enzymes, a phosphatase and a lecithinase share in this action. The latter split the phosphatide and facilitated the later action of the phosphatase.[4]

The report that follows deals with the comparative activity of enzymes derived from three species: mouse, rabbit and guinea pig. These studies may be divided into three phases: (*A*) determination of the activity of the respective enzymes on model substrates; (*B*) comparison of their effect on tubercle phosphatide and (*C*) the elucidation of differences manifested in these species.

METHODS

The methods employed were similar to those described in the earlier report (6). Three to 4 adult animals were used for the preparation of enzyme extracts from rabbits or guinea pigs. Bacteriological cultures were made on all reaction mixtures at the end of the incubation period and contaminated experiments were discarded.

RESULTS

(*A*) Since phosphatases shared in the cleavage of the tubercle phosphatide, the phosphomono- and diesterase activity of comparable extracts was determined as usual, using sodium β-glycerophosphate and the potassium salt of diphenyl-

[1] From the Laboratory of Pathology, Yale University School of Medicine, New Haven, Connecticut.

[2] These investigations have been supported by funds provided by the Research Committee of the National Tuberculosis Association.

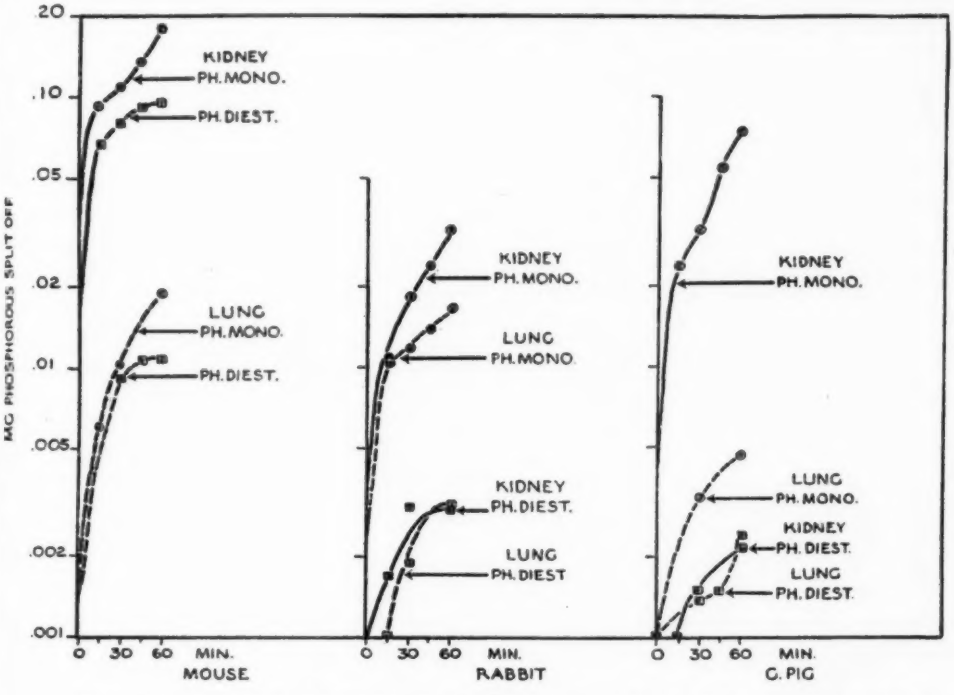
[3] Presented before the Medical Section at the 38th annual meeting of the National Tuberculosis Association, Philadelphia, Pennsylvania, May 8, 1942.

[4] McFarlane and Knight (7) have further corroborated this hypothesis of splitting phosphatides; they obtained a pure lecithinase from C. Welchii.

MG PHOSPHOROUS SPLIT OFF

orthophosphoric acid in 1/28.8M concentration as substrates. The results are included in chart I. This shows that the activity of the mouse phosphoesterases outranked those of the rabbit and even more strikingly those of the guinea pig in all instances, except the phosphomonoesterase of the guinea pig kidney. It is noteworthy that the reaction curves of the mono- and diesterases of the guinea pig and rabbit organs differed markedly.

Phosphatides other than those separated from the tubercle bacillus were also employed in determining the lecithinase activity of the various organs. Table 1 shows the results obtained with various lots of enzyme extracts on lecithin as a



REACTION VELOCITIES OF PHOSPHOMONO-AND DIESTERASES OF MOUSE, RABBIT AND GUINEA PIG

CHART I.

substrate. The incubation period in all experiments was sixty-four hours. The splitting accomplished by the different lots of enzymes varied. The lung and kidney extracts of the three species showed no essential difference. The four lots of extracts of guinea pig liver, however, were strikingly less effective in every instance than the corresponding extracts of mouse and rabbit.

Since determination of enzyme action in terms of total cleavage over an arbitrary time interval may not give a true index of activity, experiments were set up to express the cleavage of the lecithin in reaction velocities. The results are indicated in chart II. The only significant difference noted was the slight but definitely diminished initial velocity of the reaction in the case of the guinea pig organ preparations as compared with those of the rabbit and mouse.

(*B*) A comparison of the effect of the enzymes derived from the three species (mouse, rabbit and guinea pig) on tubercle phosphatide was of great interest, both from the standpoint of total cleavage and reaction velocity. Two groups

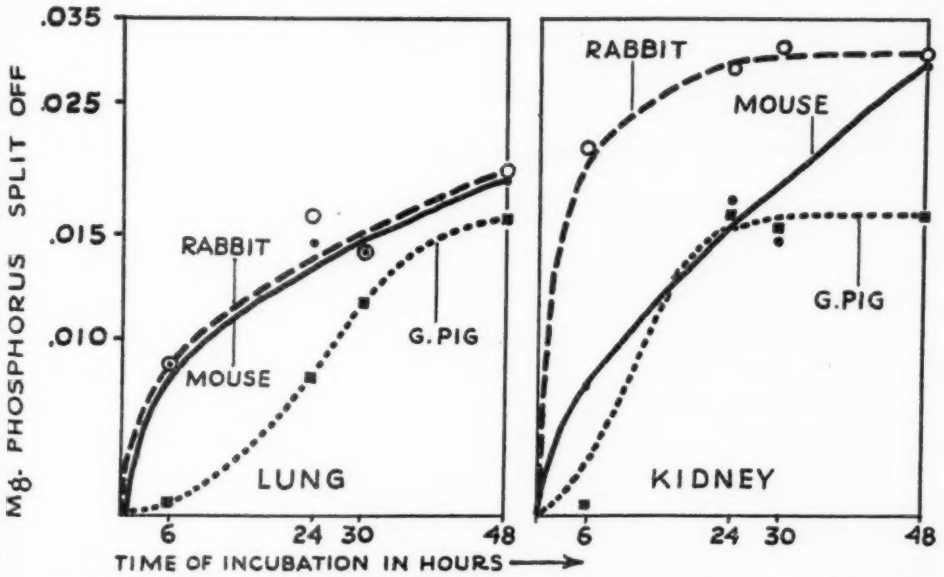
TABLE 1

ENZYME	AMOUNT OF SUBSTRATE	TIME OF INCUBATION	MG. PHOSPHORUS SPLIT OFF	SPLITTING IN PER CENT OF SUBSTRATE
	mg.	*hours*		
Mouse lung	5	64	.0730	40.5
	5	64	.0555	30.5
	5	64	.0340	18.9
Rabbit lung	5	64	.1093	60.7
	5	64	.0312 same	17.3
	5	64	.0310 powder	17.2
Guinea pig lung	5	64	.0285	15.8
	5	64	.0281	15.6
	5	64	.0433	24.1
	5	64	.0507	28.1
Mouse kidney	5	64	.1800	100
	5	64	.1560	86.6
	5	64	.0565	31.4
Rabbit kidney	5	64	.0987	54.8
	5	64	.0475	26.4
	5	64	.0923	51.3
Guinea pig kidney	5	64	.0255	14.2
	5	64	.0435	24.2
	5	64	.1585	88.1
	5	64	.0499	27.7
Mouse liver	5	64	.0744	41.3
	5	64	.0058	3.2
	5	64	.0684	37.9
Rabbit liver	5	64	.0688	38.2
	5	64	.0777	43.1
Guinea pig liver	5	64	.0000	00
	5	64	.0190	10.5
	5	64	.0060	3.3
	5	64	.0349	19.4

of experiments were carried out, one over a seven-hour period, the other over intervals comparable to those of the previous experiment. It may be seen from both experiments (seven hours and forty-eight hours, charts III and IV, respectively, especially those of the latter, (forty-eight hour period) that the mouse

enzymes split the tubercle phosphatide at a faster rate and accomplished more in a given time interval than the enzymes of either rabbit or guinea pig. The contrast was particularly striking for the guinea pig lung extract which did not split the phosphatide at all in either experiment.

This difference could not be explained by variation in concentration of enzymes since extracts of lung and kidney from all three species were capable of splitting lecithin (table 1 and chart II). Furthermore, the earlier investigations indicated that the enzymes engaged in the cleavage of lecithin and tubercle phosphatide were identical. Difference in chemical structure of the substrates suggested

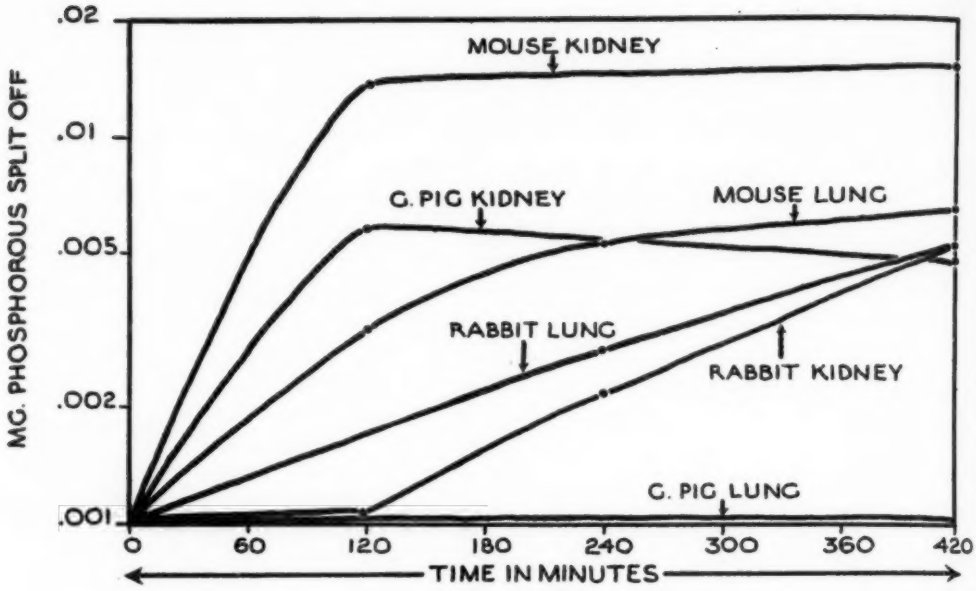


CLEAVAGE OF LECITHIN BY LUNG AND KIDNEY EXTRACTS OF MOUSE, RABBIT AND GUINEA PIG

CHART II.

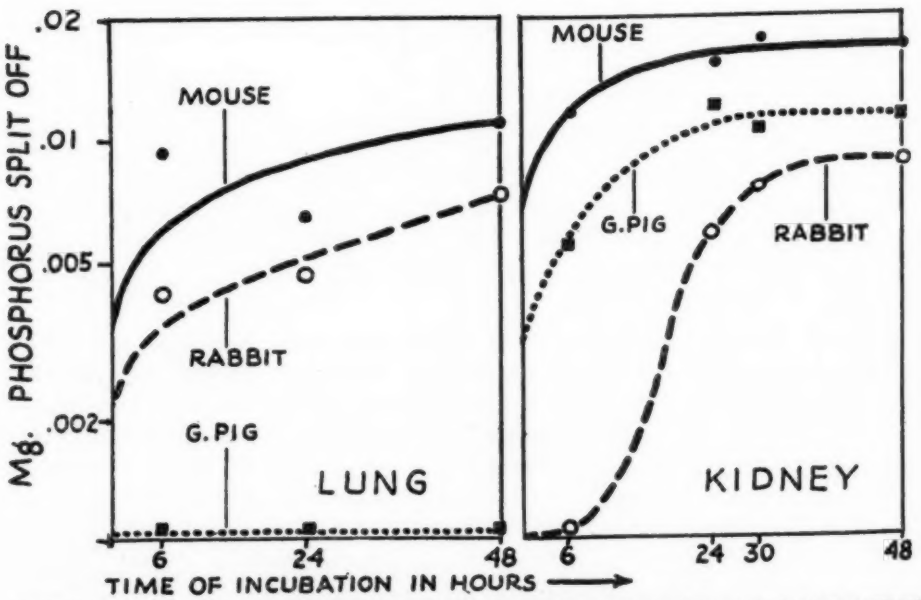
itself as one possible cause for the lack of correspondence; in lecithin, the fatty acids form esters with glycero-phosphoric acid, while in the tubercle phosphatide the fatty acids are combined with complex organic phosphoric acids and a phosphorus containing glycoside (Anderson (5)). If this were the only factor responsible for the apparent differences, a similar reduction in cleavage of the tubercle phosphatide should occur with the enzyme preparations of all the three species. This, however, was not the case.

(*C*) Another lead was obtained by the following observation. When tubercle phosphatide was added to either rabbit or guinea pig enzyme suspensions (lung) the amount of phosphorus liberated from the enzyme itself after a definite incubation time was less than in corresponding control experiments. This may be interpreted only as an inhibiting effect of the tubercle phosphatide. Coin-



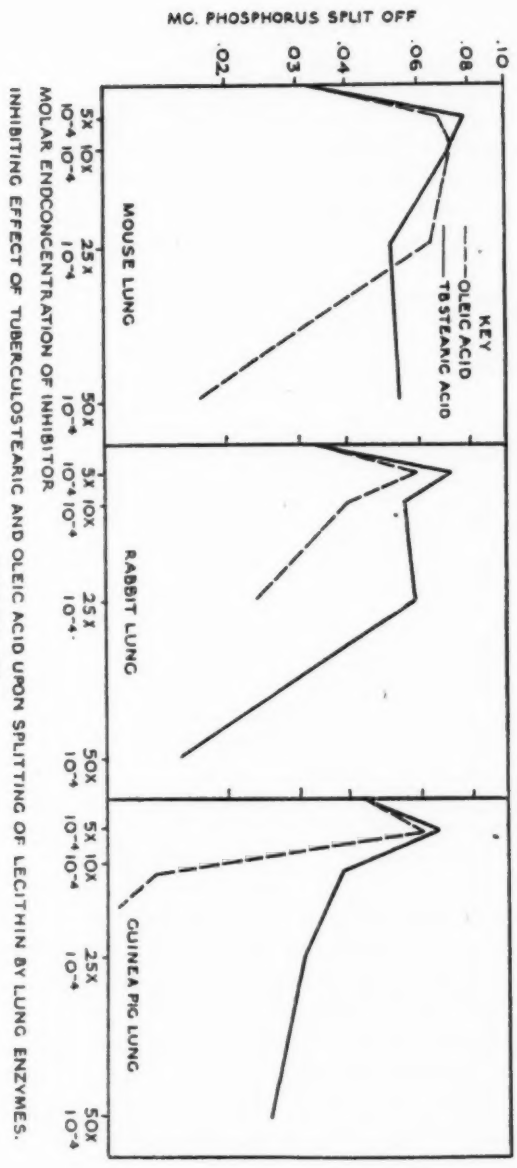
CLEAVAGE OF TB PHOSPHATIDE BY LUNG AND KIDNEY POWDERS FROM MOUSE, GUINEA PIG AND RABBIT.

CHART III.



CLEAVAGE OF TB PHOSPHATIDE BY ENZYMES OF LUNG AND KIDNEY FROM MOUSE, RABBIT AND G.PIG

CHART IV

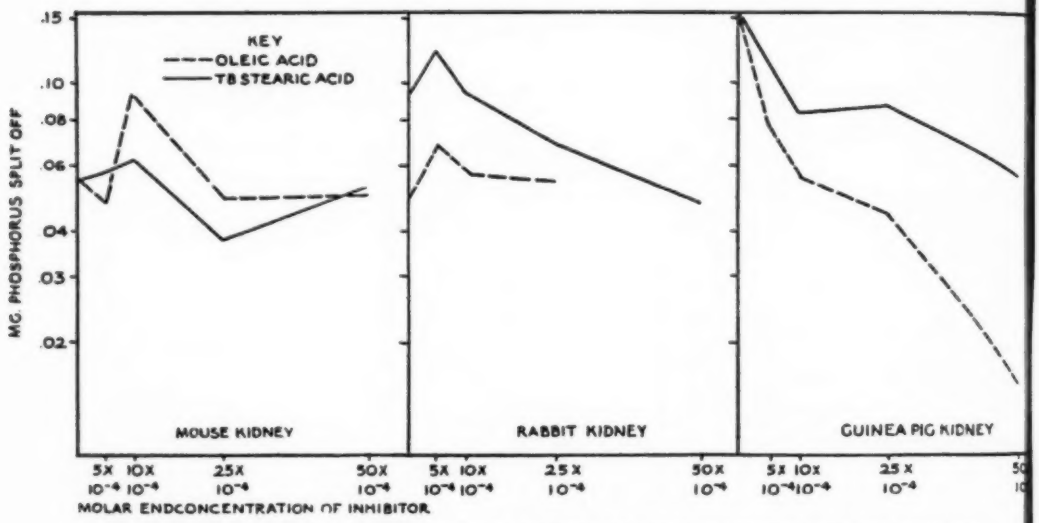


INHIBITING EFFECT OF TUBERCULOSTEARIC AND OLEIC ACID UPON SPLITTING OF LECITHIN BY LUNG ENZYMES.

CHART V.

cidentally, Peck (8) observed a similar effect of tubercle phosphatide on trypsin and recently Weiss (9) reported a similar experience with cathepsin. It seemed unlikely that the inhibition would result from the small amount of inorganic phosphorous present in the tubercle phosphatide (Anderson, *l.c.*). This was confirmed by experiments in which a corresponding amount of inorganic phosphorus failed to inhibit phosphatase activity.

Earlier observations that separation of fatty acid radicles was necessary, prior to further enzymatic breakdown of tubercle phosphatide suggested that these fatty acids might be the inhibitors. The following experiments were carried out to test this hypothesis: Aceton-ether treated powders of the lung and kidney of the three species were incubated with lecithin as substrate (enzyme



INHIBITING EFFECT OF TUBERCULOSTEARIC AND OLEIC ACID UPON SPLITTING OF LECITHIN BY KIDNEY ENZYMES

CHART VI.

concentrations, buffer and methods of estimating the amount of cleavage employed here were identical with those in the earlier experiments). Oleic acid or tuberculostearic acid (as sodium salts) in end concentrations of 5×10^{-4}, 10×10^{-4}; 25×10^{-4} or 50×10^{-4}M was added to each of the above reaction mixtures and a fifth was incubated without fatty acid to serve as control.

Oleic acid was selected because the unsaturated fatty acids found in the tubercle bacillus are mainly of this variety; the tuberculostearic acid is one of the two saturated fatty acids characteristic of the tubercle bacillus (Anderson) and was available in sufficient quantity.

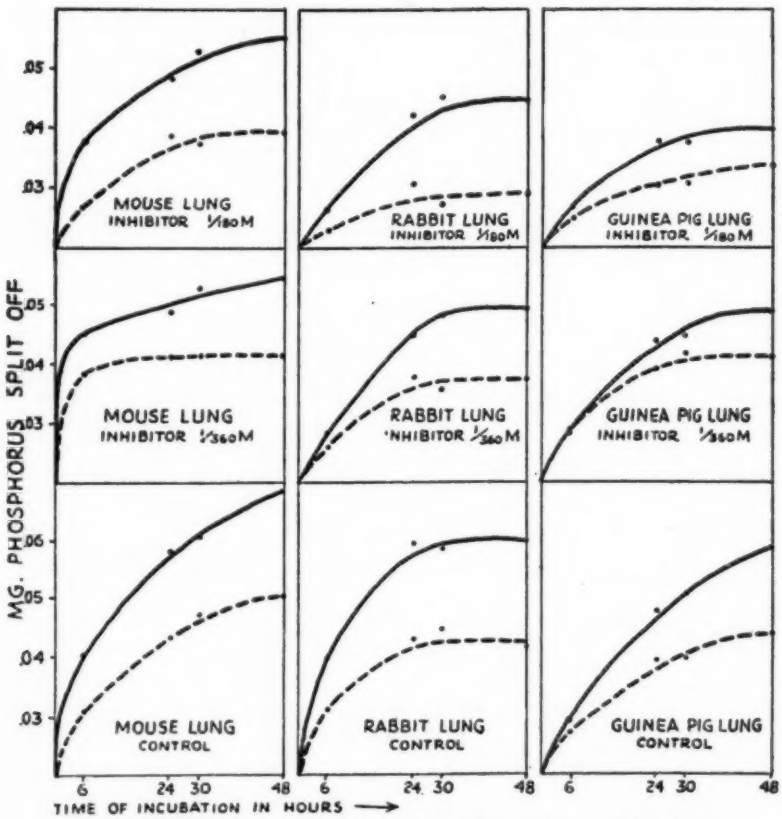
The results obtained in the first group of experiments are presented in charts V and VI. When the enzymes derived from the lungs of the three species were compared (chart V), a marked inhibition was noted for those of the rabbit and guinea pig. There was no inhibiting effect by the tuberculostearic acid on the

TABLE 2

ENZYME		CONTROL				OLEIC ACID, 1/180M				OLEIC ACID 1/360M			
		Time of incubation in hours											
		6	24	30	48	6	24	30	48	6	24	30	48
Mouse lung	Mg. phosphorus split off	.0083	.0144	.0138	.0186	.0109	.0101	.0159	.0162	.0068	.0075	.0112	.0148
	Splitting in per cent of substrate	4.7	8.0	7.7	10.3	6.0	5.6	8.8	9.0	3.8	4.2	6.3	8.2
Rabbit lung	Mg. phosphorus split off	.0091	.0163	.0139	.0179	.0031	.0117	.0181	.0167	.0019	.0070	.0121	.0118
	Splitting in per cent of substrate	5.0	9.0	7.3	10.0	1.7	6.5	10.0	9.3	1.0	3.9	6.7	6.6
Guinea pig lung	Mg. phosphorus split off	.0022	.0074	.0117	.0156	.0019	.0071	.0065	.0059	.0000	.0046	.0037	.0066
	Splitting in per cent of substrate	1.2	4.1	6.5	8.7	1.1	3.9	3.6	3.3	0	2.6	2.1	3.7
Mouse kidney	Mg. phosphorus split off	.0060	.0130	.0120	.0211	.0072	.0126	.0098	.0224	.0058	.0114	.0121	.0219
	Splitting in per cent of substrate	3.0	7.2	7.0	11.7	4.0	7.0	5.5	12.4	3.2	6.3	6.7	12.1
Rabbit kidney	Mg. phosphorus split off	.0220	.0288	.0323	.0304	.0225	.0278	.0264	.0274	.0143	.0216	.0229	.0255
	Splitting in per cent of substrate	12.2	16.0	17.9	16.9	12.5	15.4	14.7	15.2	8.0	12.0	12.7	14.2
Guinea pig kidney	Mg. phosphorus split off	.0020	.0158	.0153	.0162	.0093	.0127	.0090	.0103	.0058	.0120	.0117	.0147
	Splitting in per cent of substrate	1.1	8.8	8.5	9.0	5.2	7.1	5.0	5.7	3.2	6.7	6.5	8.2

mouse lung preparation, although the strongest concentration of oleic acid caused some diminution. When the effect of the fatty acids upon the kidney enzymes was tested (chart VI), those of the guinea pig again were found to be inhibited whereas mouse and rabbit kidney appeared unaffected.

A second group of experiments was carried out to study the inhibiting effect of fatty acids on the respective enzymes in terms of reaction velocities, since this



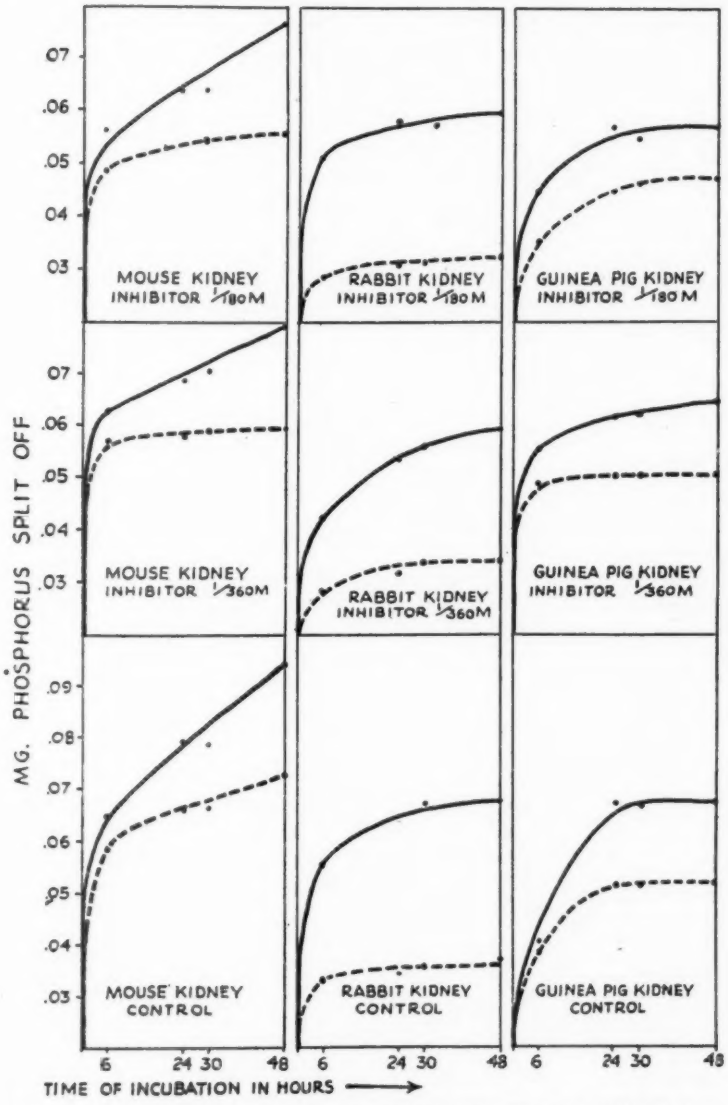
INHIBITING EFFECT OF OLEIC ACID UPON SPLITTING OF LECITHIN BY LUNG ENZYMES

CHART VII.

is a more reliable indication of the rate of enzyme activity. Enzyme suspensions, concentration of substrate and amount of buffer employed were identical with those of the former group. Oleic acid only was used as inhibitor, because of the large amounts required; this was added in end concentration of 1/180 and 1/360M. Mixtures prepared from the same lot of enzyme extracts but without the addition of oleic acid served as controls.

The results are given in table 2 and recorded graphically in charts VII and VIII. The charts are drawn in a form slightly different from those used for

former experiments. The upper unbroken line represents the amount of phosphorus split off in the reaction mixture containing both enzyme and substrate,



INHIBITING EFFECT OF OLEIC ACID UPON SPLITTING OF LECITHIN BY KIDNEY ENZYMES

CHART XIII.

while the lower curve, drawn as a broken line, represents the amount of inorganic phosphorus resulting from the breakdown of the enzyme extract itself. Hence, the direction of the curve indicates the progress of the respective re-

actions while the area between the two lines represents the amount of splitting accomplished on the substrate.

The mouse lung enzymes were only slightly inhibited by both concentrations of oleic acid in contrast to the guinea pig lung preparation which was markedly inhibited. The fermentative activity of the rabbit lung extract was impaired slightly more than that of the mouse lung. The differences were less striking for kidney enzymes. Distinct inhibition was noted only for the guinea pig kidney extract when higher concentrations of acid were employed.

The following experiment was performed to determine whether the fatty acids acted by inhibiting the phosphatases or lecithinases. Enzyme extracts of the lungs of all three species and of guinea pig kidney were incubated with sodium β-glycerophosphate as substrate to which oleic acid had been added in identical concentrations used in the previous experiments. No inhibition of phosphatase activity was demonstrable (table 3).

TABLE 3

Effect of oleic acid on phosphomonoesterase activity

ENZYME	SUBSTRATE: SODIUM GLYCERO-PHOSPHATE 1/28.8M	TIME OF INCU-BATION		CONCENTRATION OF OLEIC ACID				CONTROL
				1/200M	1/400M	1/1000M	1/2000M	
	cc.	*hours*						
Rabbit lung.....	1	1	Mg. phos-	.1152	.1537	.1500	.1530	.1399
Guinea pig lung.....	1	1	phorus	.0149	.0114			.0105
Guinea pig kidney....	1	1	split off	.0472	.0480	.0486	.0477	.0423

DISCUSSION

Enzyme activity of lung or kidney extracts from mouse, rabbit or guinea pig yielded essentially comparable cleavage of lecithin. When similar enzyme preparations acted upon tubercle phosphatide a striking difference was noted. Mouse and rabbit preparations caused cleavage of the tubercle phosphatide but the enzymes of the guinea pig lung preparation were completely inhibited. The experiments illustrated by charts V and VI demonstrated that both a saturated and an unsaturated fatty acid derived from tubercle phosphatide were capable of inhibiting lecithinase. Sheep liver esterase and pancreatic lipase have been shown similarly by Weber and King (11) to be inhibited both by unsaturated fatty acids and by aromatic acids with unsaturated side chains. The inhibition of the lecithinase demonstrated in these studies varied with the species and also with the different organs of the same species. The enzymes of the kidney, generally, were less affected. The mouse lung enzymes were noteworthy because they resist the inhibiting effect of both tuberculostearic and oleic acid.

The phosphatases were not affected by the fatty acids. This finding was in accord with Marron and Moreland's results (10) with pure phosphatases and oleic acid.

The present experiments reaffirm the importance of reaction velocity in studying enzyme activity as emphasized by numerous authors.

SUMMARY

1. The experiments reported suggest that tubercle phosphatide is broken down in the animal body by the action of two enzymes, a phosphatase and a lecithinase.

2. The action of the lecithinase prior to that of the phosphatase is essential. The activities of both of these enzymes are determining factors in the rate of cleavage of the tubercle phosphatide.

3. The fatty acids split off from the tubercle phosphatide inhibit lecithinase. This inhibition varies with particular organs and species and represents another factor associated with differences they manifest in the breakdown of tubercle phosphatide.

SUMARIO

1. Los experimentos comunicados indican que el fosfátido del tubérculo es desintegrado en el cuerpo animal por la acción de dos enzimas: fosfatasa y lecitinasa.

2. Es indispensable que actúe la lecitinasa antes que la fosfatasa. Las actividades de ambos enzimas constituyen los factores determinantes en la velocidad de la disociación del fosfátido del tubérculo.

3. Los ácidos grasos que se desdoblan del fosfátido del tubérculo inhiben la lecitinasa. Esa inhibición varía en los distintos órganos y especies y representa otro factor relacionado con las diferencias en la disociación del fosfátido del tubérculo.

REFERENCES

(1) Lurie, M. B.: Supplement to Am. Rev. Tuberc., September, 1941.
(2) Long, E. R.: Arch. Path., 1941, *32*, 122 and 286.
(3) Sabin, F. R., Doan, C. A., and Forkner, C. E.: J. Exper. Med., 1930, *52*, Suppl. 3.
(4) Lurie, M. B.: J. Exper. Med., 1942, *75*, 247.
(5) Anderson, R. J.: J. Biol. Chem., 1927, *74*, 525.
(6) Gerstl, B., and Tennant, R.: Yale J. Biol. & Med., 1941, *14*, 29.
(7) McFarlane, M. G., and Knight, B. C.: Biochem. J., 1941, *35*, 884.
(8) Peck, R.: Personal communication.
(9) Weiss, Ch.: Arch. Pathol., 1942, *33*, 182.
(10) Marron, T. H., and Moreland, F. B.: Enzymologia, 1939, *6*, 225.
(11) Weber, H. H. R., and King, C. G.: J. Biol. Chem., 1935, *108*, 131.

EXPERIMENTAL PULMONARY TUBERCULOSIS IN THE DOG[1, 2]

BCG Immunization

F. D. GUNN, J. J. SHEEHY, CHARLOTTE A. COLWELL AND M. A. MILLS

Clinical and experimental evidence on the question of the degree of immunity to tuberculosis acquired by man and various laboratory animals has been indecisive and in many instances conflicting. Most of the clinical experiments have been carried out with relatively small numbers of infants and young children of tuberculous parents and control subjects in the larger series have been improperly selected. Results from such observations have usually indicated a slightly lower mortality and morbidity from tuberculosis in the vaccinated subjects than in the controls but it is not certain that the improvement was due to the effects of immunization. In most of the published series it appears almost certain that important differences in management of the experimental groups of patients have not been taken into account by the observers. Animal experiments are much more easily controlled but the results in many cases have been uneven and difficult to interpret. The differences between the results in vaccinated and control animals have usually consisted of a rather irregular prolongation of life or diminished size of lesions in the former. Even assuming that the degree of immunity conferred by vaccination with attenuated tubercle bacilli is sufficiently great as to be decisive when infecting doses of virulent tubercle bacilli are injected subcutaneously or intravenously, this would not decide the issue of whether or not such immunity would serve to protect the individual from pulmonary tuberculosis, acquired by the intrabronchial route. Evidence on this problem must be gained either from observations on human subjects adequately controlled or from experiments on animals which manifest immunological and tissue reactions to tuberculous infection as nearly as possible identical with those observed in human tuberculosis. Neither the rabbit nor the guinea pig has met these requirements satisfactorily.

The information derived from experiments on tuberculous infection in rabbits and guinea pigs is of a general immunological nature and has not been applicable to specific problems in clinical tuberculosis. The specific immunity acquired by them is not of a very high order. The susceptibility of guinea pigs is so extreme that complete protection against virulent tubercle bacilli does not appear to be possible even when the doses are minimal. In rabbits, bacilli of greater virulence usually confer a greater degree of allergy than those of low virulence, such as BCG. It has been observed that BCG, when introduced intravenously, confers a greater degree of resistance to subsequent infection than when injected subcutaneously (Clawson (1)), although the degree of cutaneous sensitivity is less in

[1] From the Departments of Pathology, Bacteriology and Research Bacteriology, Northwestern University Medical School, Chicago.

[2] Aided by grants from the Committee on Scientific Research of the American Medical Association and from the Women's Faculty Club of Northwestern University.

the former case. According to the findings of Freund and Opie (2) there is no correlation between the intensity of sensitization or the titre of antibodies and resistance to tuberculous infection.

In the dog, an animal which successfully resists infection with tubercle bacilli of high virulence in a large percentage of cases, little has been published on the subject of artificial immunization. This animal appears to be particularly well suited for such studies since, in addition to its natural ability to bring about regression of tuberculous lesions, it develops lesions in the lung which resemble those in human subjects to a marked degree. It has been shown in previous publications (3) that cutaneous reactivity to tuberculo-protein in dogs is a reliable index of previous infection when tests are made with suitable doses of Old Tuberculin or with purified protein derivative (PPD, Seibert). In these same dogs parallel studies of antibodies with the complement fixation test (4) have demonstrated that antibody titres are roughly proportional to the intensity of the dermal reactions and that infections with virulent tubercle bacilli are accompanied by higher antibody titres than are infections with similar or larger doses of attentuated bacilli (BCG).

The data acquired from observations in dogs over a period of about six years have included, in addition to records of intracutaneous tuberculin tests and serological studies, radiographic and morphological findings in primary pulmonary infections and in reinfections with virulent tubercle bacilli after previous sensitization. The general results obtained in primary infections have been previously recorded (5). The present is concerned with comparing the results of first infection with those of infection in dogs previously sensitized to tuberculin by vaccination with BCG.

MATERIALS AND METHODS

The strain of BCG used in most of our experiments was obtained several years ago from the laboratory of Dr. W. H. Park and maintained by culture on glycerinated egg-yolk medium. In our hands it has been found to be usually harmless to adult dogs even in large doses, never leading to progressive lesions when injected intravenously, subcutaneously, intracutaneously or intrabronchially, although in a few cases the dogs inoculated with 5.0 mg. or 10.0 mg. doses seemed to be quite sick for a few days. In young puppies the symptoms were sometimes severe, with anorexia lasting for several days. The loss of weight resulted in a difference in weight between the vaccinated puppies and their sibling controls, but this difference had disappeared before the time selected for intrabronchial inoculation.

Of 17 dogs vaccinated with BCG previous to infection with virulent bacilli, 12 were full grown at the time of first injection and 5 were puppies. Each of 2 of the adults received a single 4.0 mg. dose subcutaneously and 2 were vaccinated by intrabronchial insufflation with 2.5 mg. and 4.0 mg. doses. The rest, including the 5 puppies, were injected once or twice intravenously with 5.0 mg. or 10.0 mg. doses. The puppies received their first dose of BCG when they were between seven and nine weeks old. The experiment was begun with 16 puppies, including the sibling controls, but 3 of the 8 which were injected intravenously with BCG died before the time for injection with virulent tubercle bacilli. Tuberculous lesions were found in the lymph nodes of one of these, but

its death cannot be attributed to BCG infection alone since 2 uninjected controls from the same litters died at about the same time.

All of the vaccinated dogs were tested with tuberculin[3] before injection with virulent bacilli and showed 1 plus to 3 plus dermal reactions by the Aronson standard (6). The maximal reaction was 3 plus in 4, 2 plus in 11 and 1 plus in 2 dogs. The 1 plus reactions were in 2 of the puppies which were tested before injection with virulent culture only once, fifty-six days after the first intravenous injection with BCG. The intensity of the dermal reaction may have increased between this time and the time of intrabronchial injection. With the exception of the puppies, all of the vaccinated dogs were tested with tuberculin repeatedly with both OT and PPD. In all except 2, the maximal degree of reactivity was the same as that observed just a few days before initiation of the infection with virulent bacilli. No. 30 showed a decline from 2 plus to 1 plus and no. 31 from 2 plus to negative at the time of final inoculation. All control dogs were tested before infection and all were negative.

The interval between the time of the last inoculation with BCG and the time of intrabronchial insufflation with virulent bacilli varied between eighty days and seven months. At the time of inoculation with the test dose of virulent tubercle bacilli the 10 puppies were about half grown and weighed, on the average, 7.9 kg. in the case of the vaccinated puppies and 7.2 kg. in the controls. The weights at the time of final inoculation of the full grown dogs varied between 7.7 and 17 kg. The average weight was 11.9 kg. in those which had been vaccinated and 10.7 kg. in the controls. Each of the puppies received 10.0 mg. of a bovine strain (Ravenel) as the test dose. Sixteen of the adults including the controls received 1.0 mg. of a virulent human type strain (G2) and 8 received 0.5 mg. of G2 strain per kilogram of body weight, the total dose varying from 4.0 mg. to 8.0 mg. All suspensions were made from four weeks old cultures, grown on solid medium, and the measured doses were incorporated in 3 per cent to 5 per cent mucin of which 1.0 cc. to 2.0 cc. were injected with each dose. The details of preparing and standardizing the suspensions and of the technique of inoculation have been previously described (5).

The site of the pulmonary lesions and their approximate size were determined by X-ray examination at appropriate intervals. Since our interest was centered more upon the extent and constitution of the lesions than upon the rate of mortality, more than one-half of the 34 dogs were killed with ether for the purpose of comparing the lesions of vaccinated and control dogs at various stages of their development. In the case of spontaneous death of one of the dogs, its experimental mate was usually sacrificed within a short period for comparison of their lesions.

EXPERIMENTAL RESULTS

In the tabulation of results (tables 1 and 2) we have arranged the vaccinated dogs, each opposite its unvaccinated control, in the order of the age of their pulmonary lesions. The data included are the location, type and approximate diameters of the principal lesions and the presence and relative extent of caseation, cavitation and calcification. Caseation, when present, was estimated as 1 plus (less than 25 per cent of area of lesion in microscopical sections), 2 plus (25 per cent to 50 per cent) or 3 plus (50 per cent to 75 per cent). There was no pulmonary lesion in which caseation was estimated to exceed 75 per cent. The

[3] A part of the tuberculin used in these experiments was obtained through the generosity of Dr. Esmond Long and a part was furnished by Parke, Davis & Company.

TABLE 1

VACCINATED								CONTROLS							
		Principal Pulmonary Lesions								Principal Pulmonary Lesions					
Dog Number	Survival in days	Site	Form	Diameter, mm.	Caseation	Cavitation	Calcification	Dog Number	Survival in days	Site	Form	Diameter, mm.	Caseation	Cavitation	Calcification
193	d.* 26	RML†	Solid granuloma	80 x 70 x 35				190	d. 36	RML	Caseous granuloma	20 x 18 x 12	+++		
54	s.** 30	RLL	Solid granuloma	30 x 25 x 23	+			85	s. 27	RLL	Granuloma, cavities	70 x 50 x 35	(Coagulative necrosis)	++	
58	s. 31	RML	Solid granuloma	30 x 25 x 16	++			84	d. 31	RLL	Solid granuloma	30 x 25 x 15	(Coagulative necrosis)		
57	s. 58	LLL	Scattered nodules	Up to 2				86	s. 59	RUL	Caseous granuloma	35 x 25 x 25	+++		
56	s. 62	LLL	Granuloma, cavity	40 x 35 x 20	+	++++	+	74	s. 61	RLL	Caseous granuloma	35 x 30 x 25	+++		
31	d. 132	RLL	Scattered nodules	Up to 2				36	d. 108	RLL	Necrotic granuloma	20 x 20 x 18	+	+	
30	d. 134	RLL	Granuloma, cavities	75 x 45 x 30	(Coagulative necrosis)	++++		37	s. 139	RLL	Scar				
183	d. 145	RLL	Granuloma, cavities	40 x 30 x 30	+	++++	+	186	d. 290	RML	Solid granuloma	20 x 17 x 12	++	+	+
115	s. 147	RUL	Healed cavity	35 x 30 x 20		+++		120	d. 63	RUL	Granuloma, cavities	60 x 50 x 45	(Coagulative necrosis)	++++	
9	d. 181	LML	Scattered nodules	Up to 10		+		35	s. 315	RLL	Healed cavity	16		++	
192	d. 209	RML	Granuloma, cavity	50 x 25 x 20	(Coagulative necrosis)	++++		195	d. 162	RML	Granuloma, cavities	45 x 35 x 20	(Coagulative necrosis)	++	
114	s. 210	RLL	Granuloma, cavities	Up to 15		++		122	s. 210	RLL	Healed cavities	Up to 15		++	
27	s. 265	RLL	Caseous nodule	14 x 13 x 8	+++		+	38	s. 1711	LLL	Scar				
118	s. 340	RUL	Scar					119	s. 343	RUL	Healed cavity	30 x 20 x 18		+++	
116	s. 353	RLL	Healed cavity	12 x 11 x 7		++		121	s. 350	RML	Encapsulated nodule	10	+++		+
185	s. 605	RML	Scar					187	d. 562	RLL	Encapsulated nodule	15	++		+
184	s. 606	RML	Caseous granuloma	50 x 45 x 30	++		+	188	s. 606	RUL	Healed cavity	35 x 35 x 20		+++	

*d. = died.

**s. = sacrificed.

† The abbreviations used in designating the lobes of the lungs are RUL, right upper (apical) lobe; RML, right middle (cardiac) lobe; RLL, right lower (major or diaphragmatic) lobe; Intermed., intermediate or post-cardial lobe (the medial, fourth lobe of the right lung). With the exception of the intermediate lobe, the left lung is the same, LUL, LML and LLL.

extent of cavitation was roughly estimated on the basis of the total volume of the cavity or cavities present and their relative values are indicated by plus signs. In some instances the cavities were present in secondary bronchopneumonic lesions in lobes other than that of the site of inoculation as well as in the principal lesion. In one case (dog no. 186) the principal lesion (that at the site of inoculation) was solid and the cavities were found only in the secondary lesions.

In table 2 the findings in lymph nodes, kidneys, liver and spleen are summarized. The degree of hypertrophy of the largest single tracheobronchial

TABLE 2

VACCINATED								CONTROL							
		Lymph Nodes			Hematogenous Tuberculosis					Lymph Nodes			Haematogenous Tuberculosis		
Dog Number	Survival in days	Hypertrophy	Hyperplasia*	Caseation	Kidney	Liver	Spleen	Dog Number	survival in days	Hypertrophy	Hyperplasia*	Caseation	Kidney	Liver	Spleen
193	d. 26	+	+		+	++		190	d. 36	+	+++	++	+	++	++
54	s. 30	+	+		+	+		85	s. 27	+++	+++		+	+	
58	s. 31	++	+			++	+	84	d. 31	++++	++++	+		+	+
57	s. 58	+	+					86	s. 59	+++	+++	+		+	
56	s. 62		+++			+	+	74	s. 61	+++	++++	++			
31	d. 132	+	+		+			36	d. 108		+	+	+	++	+
30	d. 134	++	+		+	+		37	s. 139						
183	d. 145		++++	+	+	++	+	186	d. 290	++	+		+	+	+
115	s. 147							120	d. 63	+++	++++	+	+	++	+
9	d. 181		++		++			35	s. 315						
192	d. 209	++	++++		++	+++	+	195	d. 162	++	+++			+	+
114	s. 210		+		+	+	+	122	s. 210		+				
27	s. 265	+						38	s. 1711						
118	s. 340							119	s. 343					+	+
116	s. 353							121	s. 350		++	+			
185	s. 605	++	++		++	+	+	187	d. 562		++				
184	s. 606	++	++		±	+		188	s. 606	+	+		+	+	

* The hyperplasia referred to in this column refers strictly to epithelioid cells which appear diffusely or in the form of discrete and confluent epithelioid cell tubercles.

lymph node or fused mass of nodes is indicated by plus signs, 2 plus representing an increase in volume of approximately ten times that of the average normal and 4 plus an increase of twenty times or more. The extent of epithelioid cell hyperplasia was estimated by examination of microscopical sections taken through the centres of the larger lymph nodes and, in most cases though not all, was found to be parallel with the degree of hypertrophy. Caseation in lymph nodes was estimated on the same basis as in the pulmonary lesions. Calcium deposits in lymph nodes were observed in only 3 cases and this item is not included in the table. Data on haematogenous foci are based largely upon estimates from microscopical sections of the degree of involvement of the various organs. Be-

sides the liver, kidneys and spleen which are the organs most commonly involved, tuberculous lesions were found in a few animals in the myocardium, adrenal, cerebrum and eye. Healed lesions in kidneys, liver and spleen, represented by areas of atrophy and fibrosis, are not included since their tuberculous origin cannot be established with certainty in every case. By the time the characteristic accumulations of epithelioid cells have disappeared, acid-fast bacilli can no longer be found in the lesions. Multinucleated giant cells of the type so commonly relied upon for making a histological diagnosis of tuberculosis in human tissues, are infrequent in tuberculous lesions in dogs and greater reliance must be placed upon the epithelioid cell tubercle for identification of the disease. The only lesion which we have encountered in dogs that has any resemblance to the epithelioid cell tubercle is the granuloma resulting from the lodgment of round worm larvae in kidneys, liver and mesenteric lymph nodes. It is only rarely that there is any great difficulty in identifying the causative agent either by the finding of acid-fast rods in the epithelioid cells of the tuberculous lesions or by the presence of larvae or their disintegration products. Tissue eosinophilia, when present, is of some assistance in the differentiation since it does not occur in tuberculous lesions.

MORTALITY FROM TUBERCULOSIS

Of the 10 young dogs which were infected by inoculation with 10.0 mg. of bovine type bacilli, 5 died of tuberculosis. Two of these, infected for the first time, died in thirty-six days and one hundred sixty-two days and 3 dogs, vaccinated with BCG about five months previous to pulmonary infection, died in twenty-six, one hundred forty-five and two hundred nine days after injection. All 3 of the vaccinated dogs were tuberculin-positive before they received their injection of virulent bacilli but 2 of them showed only 1 plus reactions when tested. Two dogs, previously injected with BCG, one subcutaneously and one intrabronchially, died in one hundred thirty-four days and one hundred eighty-one days, respectively, after intrabronchial inoculation with 1.0 mg. of human type bacilli and 2 controls died after receiving a similar dose in thirty-one and one hundred eight days. In 2 of the 4 dogs that died after receiving 1.0 mg. doses (BCG dog no. 9 and control dog no. 84), the tuberculous infection was complicated by intercurrent distemper bronchopneumonia. The evidence for this was in the appearance of mucopurulent nasal discharge and conjunctivitis a few days before death occurred and of the finding at necropsy of purely exudative lesions in the lungs in addition to the granulomatous lesions containing acid-fast bacilli. The tenth tuberculous death was in control dog no. 120 and occurred sixty-three days after intrabronchial injection of 6.5 mg. of human type bacilli. The average period of survival in the 10 dogs that succumbed to progressive tuberculosis was, for the primary infections, eighty days and for the vaccinated dogs, one hundred thirty-nine days. In addition to 10 spontaneous deaths, attributable to tuberculosis, 5 in vaccinated and 5 in controls, there were 3 in which the tuberculous lesions were judged to be insufficient to cause death. No. 31 (vaccinated), found dead one hundred thirty-two days after injection, had a

partly resolved lesion in the right lower[4] (major) lobe, consisting of several widely spaced, granulomatous nodules, 1 to 2 mm. in diameter and containing a few acid-fast bacilli. The tracheobronchial lymph nodes were only slightly enlarged and contained a few epithelioid cell tubercles. Minute tuberculous foci were found also in microscopical sections of the kidneys. Dog no. 186, an unvaccinated dog, was killed with ether two hundred ninety days after intrabronchial inoculation with 10.0 mg. of bovine type bacilli because of its inability to stand or eat during the preceding three days. There was no loss of weight from the time of inoculation to the time of death (7.25 kg. to 7.53 kg.) but it had not gained at the rate expected of a young dog. Necropsy revealed a partly encapsulated caseous chalky lesion in the right middle (cardiac) lobe and a few small (up to 2 mm. diameter) granulomatous nodules in other areas. Microscopical sections showed epithelioid cell tubercles in the tracheobronchial nodes, kidneys, liver, spleen and a single minute focus in the cerebral cortex but no meningitis. No. 187 (unvaccinated) gained about 1.5 kg. between the time of injection and the time of death, five hundred sixty-two days later. Its tuberculous lesions consisted of a caseous chalky nodule, almost completely surrounded by a dense fibrous capsule, and a small granuloma, completely encapsulated, in one of the tracheobronchial nodes. With the exception of thickening and fibrous adhesions of the pleura no other lesions were found. While some doubt may be entertained regarding the responsibility of tuberculous infection for the death of BCG dog no. 31 and for the moribund state in control dog no. 186, there can be little doubt that no. 187 died from some cause other than tuberculosis since the only tuberculous foci were small and successfully arrested. If we exclude no. 187 alone from the mortality figures, the possible deaths from tuberculosis still remain equal, 6 out of 17 in vaccinated dogs and the same in controls, and the average survival periods for dogs that died or were sacrificed while moribund are one hundred thirty-eight days for BCG dogs and one hundred fifteen days for controls.

COMPARISON OF LESIONS

The differences in diameters of the pulmonary lesions are so irregular that no definite trend can be observed. In some of the pairs the more massive lesions are found in the vaccinated dogs and in others the lesions of unvaccinated dogs are the larger. In approximately one-half of the pairs the pulmonary lesions are nearly of the same size. The more extensive lesions in each group occurred usually in the dogs that had received the larger doses of tubercle bacilli.

True caseation was found in the pulmonary lesions of 6 vaccinated dogs and in 7 of the controls. The degree of caseation was, in general, slightly greater in the primary lesions (3 plus in 4, 2 plus in 2 and 1 plus in 1) than in those of infection following vaccination (3 plus in 1, 2 plus in 2 and 1 plus in 3).

Cavity formation occurred with almost equal frequency in previously sensitized and control dogs, occurring in 8 dogs of the former group and in 9 of the latter if

[4] In order to minimize confusion, the terminology used for designating the lobes of the dogs' lungs conforms as far as possible to that used for the human lung.

we include bronchiectatic cavities of microscopical size in one dog from each group.

Complete inactivity of the pulmonary lesions as evidenced by conversion of the lesion or lesions into solid scars or into completely fibrous, cyst-like cavities was observed in 7 of the 34 dogs, 3 in vaccinated and 4 in controls.

A pair by pair comparison of the diameters of the tracheobronchial lymph nodes shows that the largest single node was larger than that of its experimental mate in 10 of the previously vaccinated dogs and in 7 of the controls. This kind of comparison gives an inaccurate view, since in several pairs the differences are very slight and the diameters are within normal limits. Among the 17 previously vaccinated dogs the diameters of the largest nodes of 7 were within normal limits and 5 were only moderately enlarged, leaving 5 that showed pathological hypertrophy of significant degree. In the 17 controls there were 10 in which the size of the nodes was within normal limits or only moderately enlarged. In the remaining 7 the nodes showed a high degree of hypertrophy and hyperplasia and in 5 of these the degree of involvement was greater than that found in any of the vaccinated dogs. Caseation involved the regional nodes in 7 of the controls and in only one of the vaccinated dogs. Five of the 8 dogs in which caseous nodes were found had died of tuberculosis. Five of the unvaccinated dogs which had caseous lesions in the nodes had died or were sacrificed within sixty-three days of the time of injection.

Haematogenous lesions in liver, kidneys and spleen were present in about two-thirds of the dogs and involved members of the two groups with approximately equal frequency. Epithelioid cell tubercles were found in the kidneys of 10 vaccinated and in 6 control dogs; in the liver of 10 vaccinated and 10 control dogs; in the spleen of 6 of the vaccinated and in 7 of the controls. No tuberculous foci were found in any organ outside of the pulmonary complexes in 5 of the vaccinated and in 7 of the controls. These were without exception dogs in which the pulmonary lesions were either completely healed or successfully arrested. Pleural effusion was observed at necropsy in 4 of the unvaccinated dogs dying at the end of thirty-six, sixty-three, one hundred eight and one hundred sixty-two days and in none of the previously vaccinated dogs.

DISCUSSION

Since the experiment was planned for the purpose of studying lesions at various stages rather than the effect of vaccination upon mortality from tuberculosis, the comparative death rate should not be considered as of major importance but rather as suggestive only of what may be expected in experiments using larger numbers of animals and planned for the purpose of ascertaining the effects of vaccination upon survival time and mortality rate. The fact that the spontaneous deaths from tuberculosis in the two groups of experimental animals were equal in number suggests that the differences in average survival time may have been purely fortuitous. The difference is not consistent in each pair and the number of dogs in the experiment is not sufficiently large to justify a definite

decision. On the other hand, it has been observed in a series of more than 200 dogs with tuberculous infections that pleural effusion has occurred more frequently in association with the early stages of primary infections than with the lesions of reinfection, and it may be that the earlier death in dogs infected for the first time is in some degree dependent upon a more readily involved and a more frequently perforated pleura. Massive effusion, either with or without pneumothorax, is usually fatal within a short time in dogs. In these 10 deaths directly attributable to tuberculosis, effusion was an important factor in the fatal outcome in 4 and all 4 were in primary infections.

Positive evidence of the effects of allergy and immunity in the dogs which were vaccinated with BCG previous to intrabronchial inoculation with virulent tubercle bacilli is relatively slight and consists of slightly less caseation in the pulmonary lesions and a milder degree of hypertrophy, hyperplasia and caseation in the tracheobronchial lymph nodes during the first two months of the disease. This corresponds approximately to the period during which the infected dogs develop a maximal degree of allergy and immunity. Significant differences between the lesions in the nodes in vaccinated and control dogs are not apparent after a period of about one hundred days and in most of the lesions the stage of maximal hypertrophy and hyperplasia has been passed by this time. The occurrence of caseous necrosis parallels roughly the degree of granulomatous hyperplasia and therefore in this particular group caseation is found most often in unvaccinated dogs in the earlier stages of development of the disease. The number of animals upon which this observation is based is not sufficiently large to justify a generalization upon this point.

In spite of the fact that the regional lymph nodes of the vaccinated animals showed a milder degree of hyperplasia and less necrosis during the first two months' period than did those of the controls, blood-borne generalization, as indicated by the presence of tuberculous lesions in the liver, kidneys and spleen, was no less frequent in the former. To explain this, one must assume either that the acquired tissue immunity is of a very low order, insufficient to block the passage of tubercle bacilli through the lymphatic filters, or else that the bacilli enter the blood stream through the walls of pulmonary capillaries and venules without having passed through the lymph channels. The evidence at hand on this question is inconclusive.

Probably the most important finding in this experiment is that the greatest degree of allergy and immunity obtained in these dogs by previous injection of one or two doses of living BCG was insufficient to influence significantly the development of pulmonary lesions when the infective inoculum was introduced by intrabronchial insufflation. This observation, if confirmed by further work, would indicate that the natural resistance of young or fully mature dogs to this form of tuberculous infection, which is of a very high order, cannot be further enhanced by injections of living attenuated tubercle bacilli (BCG), even though specific antibodies are present in the serum and hypersensitivity, as indicated by dermal reactivity to tuberculin, is developed to a considerable degree.

SUMMARY

In dogs which have been inoculated intravenously, subcutaneously or intrabronchially with living cultures of attenuated tubercle bacilli (BCG) the results of intrabronchial inoculation with virulent tubercle bacilli have been compared with those in controls which have not been previously vaccinated. The mortality attributable to tuberculosis was the same in vaccinated dogs as in unvaccinated controls. The average survival time in dogs which died of tuberculosis was longer in vaccinated than in controls but the individual differences were so great that the averages probably have no significance.

No consistent differences in the size or composition of the pulmonary lesions in members of the two groups, examined at various intervals from the time of inoculation, were observed. Caseation and cavity formation occurred with about equal frequency in the two groups but caseation was slightly more extensive in the primary lesions of the unvaccinated dogs. The degree of hypertrophy, hyperplasia and caseous necrosis of tracheobronchial lymph nodes was greater in controls than in vaccinated dogs during the first two months' period but after this time these differences tended to disappear.

SUMARIO

En los perros inoculados por vía intravenosa, subcutánea o intrabronquial, con cultivos vivos de bacilos tuberculosos atenuados (BCG) se comparó el resultado de la inoculación intrabronquial de bacilos tuberculosos virulentos con el obtenido en los testigos que no habían sido previamente vacunados. La mortalidad imputable a la tuberculosis fué idéntica en ambos grupos. El tiempo medio de sobrevivencia en los perros que murieron de tuberculosis fué más largo en los vacunados que en los testigos, pero las diferencias individuales fueron tan grandes que los promedios probablemente carecen de importancia.

No se observaron diferencias en el tamaño o composición de las lesiones pulmonares en los componentes de los dos grupos, examinados a varios plazos desde el tiempo de la inoculación. En los dos grupos alcanzaron frecuencia igual la caseación y la formación de cavernas, pero la primera fué algo más extensa en las lesiones primarias de los perros no vacunados. El grado de hipertrofia, hiperplasia y necrosis caseosa de los ganglios linfáticos tráqueobronquiales fué mayor en los perros testigos que en los vacunados durante los primeros dos meses, pero después de esa época tendieron a desaparecer dichas diferencias.

REFERENCES

(1) Clawson, B. J.: Arch. Path., 1935, *20*, 343.
(2) Freund, J., and Opie, E. L.: J. Exper. Med., 1938, *68*, 273.
(3) Colwell, C. A., and Mills, M. A.: Am. Rev. Tuberc., 1940, *42*, 259 and 271.
(4) Shepard, C. C., Jung, R. W., Colwell, C. A., Gunn, F. D., and Barth, E. E.: Ibid., 1941, *43*, 825.
(5) Mills, M. A., Barth, E. E., and Gunn, F. D.: Ibid., 1940, *42*, 28.
(6) Aronson, J. D.: Ibid., 1934, *30*, 727.

GASTRIC LAVAGE IN HEALTHY ADOLESCENTS[1]

A Bacteriological Study of Fasting Gastric Contents for Tubercle Bacilli

C. FLOYD, H. A. NOVACK AND C. G. PAGE

For several years, in the search for the early case of pulmonary tuberculosis, large groups in the population have been investigated clinically and by laboratory methods. In some cities the work has been productive of striking results.

The Army Induction Service, through its general use of X-ray films has brought to light many symptomless cases of early phthisis. The extension of this work to include the examination of large numbers of sputum specimens from the apparently nontuberculous, or of the gastric contents, promises to show sources of infection ordinarily unsuspected.

The bacteriological study of the fasting gastric contents for tubercle bacilli has been repeatedly demonstrated to be of great value and often productive of positive results when other methods have been negative. In this report this proceedure was used in a search for tubercle bacilli in a group of 219 well persons between the ages of sixteen and twenty-six, in whom there was a known or suspected contact with pulmonary tuberculosis. Of these, 78 were male and 141 female. In many, the exposure had ended several years previously, while in others it was much more immediate.

As would be expected, tuberculin reactions were irregular. Following the initial exposure it appeared promptly only later to become negative, or a negative test was obtained for several years before a positive one occurred. One hundred and eighty tests were positive and 39 negative, although in the latter the X-ray film showed small calcified nodes in many instances.

The X-ray picture of the entire clinical material is a composite one, in that serial films have been taken over a period of from one to fourteen years, the average being six years. In only one case was an epituberculous lesion noted. Fifty-nine showed calcification in the right or left hilar nodes and in 3 a primary calcified focus appeared in the lung parenchyma. One hundred and thirty cases maintained a consistently negative series of films throughout the entire period of observation. Where a primary focus was found, several years elapsed between the time it was first detected and the present study and in every case it appeared obsolete. In none of this group were areas of calcification laid down following the initial lesion.

Among 219 selectees, 156 had the fasting gastric contents studied once, 52 were analyzed twice and in 11 cases where the results were most suggestive, 3 examinations were made.

METHODS

To secure the gastric contents a tube was passed through the nose into the stomach. About 40 cc. of sterile buffered saline was injected and this solution sucked back and forth several times before it was finally removed for examination.

[1] From the Boston Health Department, Boston, Massachusetts.

In the first 200 specimens obtained, the material was thoroughly centrifuged and the sediment mixed with an equal volume of 5 per cent oxalic acid according to the method of Corper. In the next 86 specimens, following centrifugalization, the sediment was treated with an equal volume of a 3 per cent solution of sodium hydroxide. Direct smears of each specimen were stained by Petroff's method. The remaining material was neutralized and planted on potato media with and without glycerine and also on egg-yolk slants. Loewenstein's medium, as modified by Jensen and Holmes, was also used.

Two guinea pigs were inoculated with the treated sediment, one intraperitoneally and the second subcutaneously in the left groin. No animal was sacrificed in less than six weeks. In a number of instances, where the animal inoculated subcutaneously appeared healthy after two months time, fresh material from the same patient was injected into its peritoneal cavity.

The laboratory data derived from smears of centrifuged gastric contents, cultures, autopsy findings and pressure smears from any enlarged lymph nodes and from the spleen in each animal were all negative. In 2 instances only were acid-fast bacilli obtained on direct smear. Cultures were uniformly negative for tubercle bacilli, not only when planted directly from stomach washings but also from enlarged mesenteric lymph nodes and from the spleen. In animal inoculations 471 guinea pigs were used. In no instances were typical tuberculous lesions demonstrable, in spite of a period of observation of from six to twenty weeks.

Nine hundred and forty-two pressure smears were made from guinea pig spleens. Of these, 81, or 8.5 per cent, showed acid-fast bacilli. The organisms frequently looked like typical tubercle bacilli, or they were partly acid-fast rods with acid-fast granules. In some smears, phagocytosis had taken place and in others the organisms were in the centre of a mass of round cells; in others they were free in distribution with no apparent cellular reaction.

Cultures were made on Loewenstein's media from 15 spleens showing acid-fast organisms, but these were all negative. In 10 instances macerated splenic pulp was injected into the peritoneal cavity of guinea pigs. All these tests were negative.

In 1928 Cooper and Petroff reported the finding of acid-fast bacilli in lymph nodes of guinea pigs which had been inoculated with filtered tuberculous material. No lesions of tuberculosis were noted and all cultures were negative. In 33 per cent of a small series of uninoculated animals, acid-fast rods were demonstrated without any pathological lesions.

While our results in inoculated animals approximate those of Cooper and Petroff in that no tuberculous lesions were found and the cultures were uniformly negative, it should be noted that this series is much larger; the acid-fast forms showed more variation; some phagocytic action was present and cellular reaction occurred. Furthermore, in 9 tests there were suspicious smears in each of 2 concomitant animals; in 3 tests this occurred three times and in 2 tests four times.

However, the proof of the presence of viable tubercle bacilli in the gastric contents of any one of the entire group of 219 is lacking, inasmuch as no character-

istic lesions of tuberculosis were obtained throughout this series of inoculations and all cultures were negative.

These results may be in part accounted for by the chemical solutions used and also by the fact that, even if tubercle bacilli were present, they were in all probability in very limited numbers, in individuals who showed no clinical or X-ray evidence of active disease.

CONCLUSIONS

It has been impossible to demonstrate tubercle bacilli in the gastric contents of a group of normal adolescents and young adults.

In a small percent age of animals inoculated with gastric contents, acid-fast bacilli were demonstrated at autopsy which could not be cultured and which were not associated with any lesions suggestive of tuberculosis.

CONCLUSIONES

Fué imposible encontrar bacilos tuberculosos en el contenido gástrico de un grupo de adolescentes y jóvenes normales.

En un pequeño porcentaje de los animales en que se inoculó contenido gástrico, se encontraron en la autopsia bacilos ácidorresistentes que no pudieron ser cultivados, y que no se asociaban con lesiones indicativas de tuberculosis.

BIBLIOGRAPHY

(1) Cooper and Petroff: J. Infect. Dis., 1928, *43*, 200.
(2) Saenz, Coste and Costil: Compt. rend. Soc. de biol., 1933, *3*, 934.
(3) Poulsen, Valdemar and Anderson: Am. J. Dis. Child., 1934, *47*, 307.
(4) Valtis and Van Denise: Compt. rend. Soc. de biol., 1935, *119*, 933.
(5) Kahn and Nonidez: Am. Rev. Tuberc., 1936, *34*, 361.
(6) Armand-DeLille and Kerambrun: Bull. Acad. de méd., 1936, *115*, 467.
(7) Corper: J. Lab. & Clin. Med., 1938, *23*, 1195.
(8) Rosencrantz and Hurwitz: Am. Rev. Tuberc., 1940, *41*, 645.
(9) Roper and Ordway: Ibid., 1941, *43*, 543.
(10) Steenken and Smith: Ibid., 1941, *43*, 307.
(11) Petroff: Quart. Bull. Sea View Hosp., January, 1939; January 1940.
(12) Am. Trudeau Soc. Rep., Am. Rev. Tuberc., 1942, *45*, 157.

ATYPICAL FINDINGS ON ANIMAL INOCULATION[1]

S. E. FRANCO AND J. GUREVITCH

In the biological test for tuberculosis, the injection into guinea pigs of urine sediment containing small quantities of tubercle bacilli may sometimes produce an atypical reaction. Such a reaction may lead to a negative diagnosis in an individual undoubtedly suffering from tuberculosis of the kidney.

The following is a brief report of such a case.

The patient was a male, thirty-four years old, a factory clerk. In early childhood he had scrofulosis. At the age of twenty-five his inguinal lymph nodes were found enlarged for no apparent reason. Four years later haematuria appeared and recurred two to three times a year during the following three years. Several examinations of the urine were made, but only in one instance were a few tubercle bacilli found. At that time the patient was treated and was apparently in good health for about three years. In March, 1939 the haematuria reappeared, accompanied by pains in the loins, vomiting and a sensation of oppression. A urine examination revealed the presence of acid-fast bacilli. A cystoscopic examination was suggested but the patient refused to submit to this procedure. Radioscopy showed calcification of the paravertebral and mesenteric nodes. X-ray films with uroselectan revealed scanty renal secretion and dilatation of one of the ureters.

On June 6, 1939, a specimen of urine was sent to our laboratory for the first time. The findings were as follows: albumin, 0.5 per mil.; sediment, large number of leucocytes and a few acid-fast bacilli, found only after a long and thorough search. On the same day a culture was made and 1.5 cc. of urine sediment were inoculated into the peritoneal cavity of an adult guinea pig. Neither the urine nor the sediment had been subjected to any preparatory treatment. During the following seven weeks the guinea pig remained well and showed no signs of disease except for slight loss in weight.

The guinea pig was sacrificed and on autopsy small white-grayish spots were found on the surface of the liver and spleen. The spleen was slightly enlarged. There were no changes of the peritoneum, lymph nodes or any other organ or tissue. Smears and sections from the spots on the spleen and liver were carefully examined but no tubercle bacilli were found.

In sections of the liver some lesions were found in the periportal spaces, which were very much enlarged owing to the presence of a great number of lymphocytes and marked hyperplasia of the cells of the connective tissue. These elements were not arranged in any regular way and formed no nodules.

In sections of the spleen marked development of the germinal centres of the follicles was noted, accompanied by hypertrophy and hyperplasia of the cells of the reticulum, principally immediately beneath the capsule. The spleen did not present any nodular formation.

[1] From the Hadassah Rothschild University Hospital, Jerusalem.

The result obtained suggested a simple nonspecific reaction to an inflammatory, slowly acting, mild irritation. In view of the fact that urine, containing typical acid-fast bacilli, failed to produce any specific lesions in the guinea pig seven weeks after inoculation, it was decided to repeat the experiment.

Two adult guinea pigs were inoculated in the same way with sediment from the same patient. One of the animals succumbed a month after the inoculation. In both animals typical tuberculous changes were found in the liver, spleen, peritoneum and mesenteric nodes. In smears and histological sections many tubercle bacilli were found.

Three months later two seven to eight months old hamsters (*cricetus auratus*) and two guinea pigs were again inoculated with the urine of this patient. One of the hamsters was found dead three and a half months later and, as putrefaction had already set in, autopsy was impossible. The other hamster died exactly five months after inoculation and typical tubercles were found in the liver and spleen with many tubercle bacilli in smears and sections. Of the two inoculated guinea pigs one was positive and the other negative.

Repeated cultures of the urine on Loewenstein's medium remained sterile. Growth of tubercle bacilli was obtained from the spleen and liver of the positive animals. In order to determine whether the strain was of the human or bovine type it was inoculated intravenously in a rabbit. The animal showed no signs of disease, gained in weight and, when sacrificed after a period of five months, no tuberculous lesions were found. Evidently the strain was of the human type.

Recently another similar case occurred. A child seven years old, with a negative personal and familial history, developed half a year previously swellings of the lymph nodes of the neck on both sides with abscess formation, general malaise and fever up to 40°C. Mantoux reaction was strongly positive.

On November 9, a very small mass of white-grayish material from the fistula of the node was brought for examination. Microscopically no tubercle bacilli were found. Cultures remained negative. A guinea pig inoculated on the same day and sacrificed two months later showed no signs of tuberculosis. Six weeks later another specimen of pus from the fistula was sent for examination. This time, microscopical examination revealed isolated acid-fast bacilli. The material was inoculated into a guinea pig and when sacrificed two months later, it was found to be normal.

Because of the scarcity of material only one guinea pig was inoculated each time. The patient received intensive treatments—among others X-ray—and when last seen on March 12 was in good health. The affection of the lymph nodes on both sides was found apparently healed and no more matter for further examinations could be obtained.

It appears that there is variable resistance in guinea pigs which manifests itself when small numbers of tubercle bacilli are present in the inoculum. Consequently in order to avoid erroneous results the following may be suggested:

1: A large quantity of the material under examination should be inoculated,
2: In such cases several guinea pigs should be inoculated simultaneously,
3: The animals should not be sacrificed in less than two months from the date of the inoculation.

SUMMARY

Two cases are reported in which inoculation into guinea pigs of material apparently containing tubercle bacilli did not produce inoculation tuberculosis.

SUMARIO

Comunícanse dos casos en los que la inoculación en el cobayo de material que aparentemente contenía bacilos tuberculosos, no produjo tuberculosis de inoculación.

PNEUMOTHORAX TREATMENT[1, 2]

The Subsequent History of Tuberculous Patients after Their Selection for Pneumothorax

W. H. MORRISS

Pneumothorax therapy like many other methods of treatment has run a clinical course characterized by slow onset, when recognition and utilization were scant, a florid middle period of great enthusiasm and a later period of partial disappointment and destructive criticism. To one, who has for twenty years witnessed the many benefits of pneumothorax treatment as well as some of its failures and disasters, it seems that the present fashion of criticism is perhaps overly harsh. Is there not danger that many patients may be denied the well established benefits of pneumothorax through undue apprehension of grievous complications on the part of their medical attendant?

Our experience with pneumothorax at Gaylord Farm is a comparatively long one and, due to the small geographical district from which we draw our patients, our recording of the follow-through and follow-up results is unusually complete. A presentation of our results, therefore, seems worth while even though the literature is already overburdened[3] with statistical surveys. It is with no ambition to present a set of results that will meet the criticism of our statistically minded colleagues that I offer this paper, rather it is my desire to give the clinician a carefully verified report of what has happened to a fairly large number of pneumothorax cases which he may use as a basis to determine what is to be expected in the way of restitution to a working capacity under normal conditions of living. In addition, I shall point out the incidence of hazards that pertain to this treatment and attempt to analyze the factors that influence the prognosis favorably or unfavorably.

It is well to recognize that any reporter of statistical end-results of the treatment of tuberculosis will encounter difficulties inherent in the nature of the disease. Such reports of results are simple in most surgical conditions and in acute infections, for the patient either recovers or dies. In reporting end-results in the chronic disease like cancer, syphilis, diabetes or tuberculosis the conditions imposed are much more difficult to handle. Five year cures are acceptable in many forms of cancer, but five years of comparatively good health may be but an incident in the history of a tuberculous infection in any one individual. In the great majority of cases only the years of a life time can tell the final story.

This study, while far from satisfactory from the point of view of elapsed time, has been of sufficient duration to give it certain weight. In the group later re-

[1] Presented before the Medical Section at the 38th annual meeting of the National Tuberculosis Association, Philadelphia, Pennsylvania, May 7, 1942.

[2] From the Gaylord Farm Sanatorium, Wallingford, Connecticut.

[3] Bloch *et al.* (J. Thoracic Surg., 1941, *10*, 313) estimate that 2,100 publications have been made on the subject of air collapse during the decade of 1929 to 1939.

ported in detail all patients who survived have been followed for a period averaging seven and one-half years from the institution of treatment and five and one-half years from its discontinuance; 77 patients have been followed for over ten years and the shortest time of follow-up is from two to three years for 6 cases.

Between the dates of 1921 and 1939, 770 patients were selected for pneumothorax treatment. These cases are divided into groups in table 1 that presents a summary of their survival and mortality. Of the entire group, 112 cases (group 2) had no free pleural space and were rated as unsuccessful. This is 14.5 per cent of failure at the onset. Another 45 cases were discontinued in less than three months as entirely ineffective. This adds another 5.8 per cent to the list of technical failures. Of the remaining 613 cases, 243 are not adequately traced as they left the sanatorium for various reasons and had their pneumothorax carried on elsewhere. This group has only 26 recorded deaths, which is certainly too few and should, on the basis of the record of the remaining 370 cases, have a

TABLE 1

770 cases selected for pneumothorax

PNEUMOTHORAX	TOTAL NUMBER	LIVING	NUMBER DEAD	PER CENT DEAD
Longer than three months	370	295	75	20.3
Unsuccessful	112	76	36	32.1
Discontinued as ineffective under three months.	38	14	24	63.1
Discontinued under three months, not traced.	7	7 ?	0 ?	0.0
Continued elsewhere, partially traced	243	217	26 ?	10.7 ? (20.0)
Total	770	609	161	20.9

mortality of at least 48, or 20 per cent. The group of 370 cases that were carried on at the sanatorium and after discharge at the ex-pateint clinic are reported in detail.

One of the many difficulties encountered in attempting to assess the value of pneumothorax by a survey of end-results has been the lack of an adequate control. The use of the unsuccessful group as such a control has been criticized and is open to such questioning, for the very fact that no free pleural space could be found indicates that these patients have had an adhesive pleuritis in addition to intrapulmonary disease. However, such an old pleuritis in itself does not usually affect the prognosis seriously. Without unduly stressing this comparison I compare in the last table the end-results in this series of unsuccessful cases with the results attained in the 370 successful cases to be reported in detail.

In most ways this group of unsuccessful cases is comparable with the successful group; thus of group 1, the successful group, 0.4 per cent were minimal, 55.9 per cent moderately advanced, and 43.7 per cent far advanced; as contrasted with 2.7 per cent minimal, 56 per cent moderately advanced and 41.7 per cent far

advanced in group 2. In group 1, 81.6 per cent had a positive sputum at the onset of treatment against 80 per cent in group 2; 38.6 per cent in group 1 had cavitation over 2 cm. in diameter and 30.6 per cent in group 2. If anything, group 1 is a little the worse group. In group 2, after the failure of pneumothorax, other collapse methods were used in about half of the cases, phrenic interruption in 35 cases and thoracoplasty in 19.

METHODS

The group of 370 cases reported in detail was treated at the Sanatorium with a combination of collapse and rest regimen usually consisting of at least two months of bed-treatment followed by a program of gradually increased activity up to one or two hours exercise. Refills were given at time intervals varying from twice a week to once every two or three weeks. The amount of air introduced varied between 100 and 600 cc. Each case was given careful individual attention as regards dosage of air and frequency of refill under fluoroscopic and roentgenographical control. The objective was to produce and maintain a collapse sufficient to control the diseased portion of the lung and leave uncollapsed, whenever possible, the more normal portions; in other words, a selective collapse was sought. After discharge from the Sanatorium, the patients returned for their refills and were thus kept under frequent supervision for the entire period of their treatment. After the pneumothorax was discontinued the patients were still followed at the ex-patient clinic and were advised as to their rehabilitation.

DEFINITIONS

Pneumothorax is listed as *unsuccessful* when no free pleural space could be found or no pleural separation demonstrated by X-ray.

The term *effective* is employed when a sufficient degree of pulmonary collapse is obtained to apparently close cavities and bring about an adequate collapse of the diseased portions of the lung. Clinical results such as disappearance of symptoms and disappearance of bacillary sputum are not included in the term as here used, for an attempt is being made to keep this an anatomical definition.

The classification of the National Tuberculosis Association is employed as defined at the time the case was under treatment.

Cases are grouped as *sputum-negative* when no tubercle bacilli could be found in serial direct smears or in smears from concentrate. Culture, animal inoculation or gastric lavage methods were not used.

Contralateral lesion is listed as *slight* when within the limits of the N. .T A. definition of a minimal lesion.

The time of closure of cavity is a rough approximation, as it is judged by the disappearance of the cavity in X-ray films and these films were usually taken at two-month intervals.

Effusions are listed as *trace*, *slight* or *large*. All cases showed at some time in the collapse period at least a trace of effusion in the costophrenic angle. When the effusion covered the dome of the diaphragm and reached to the level of the

ninth vertebral spine it is rated as large. *Empyema* is judged present when the exudate became frankly purulent or markedly turbid and contained bacilli.

Marked symphysis is used to designate the cases in which pleural adhesions increased sufficiently to prevent an effective collapse.

Working full time: The use of the term "working" as an indication of the patient's condition has been criticized, as it is stated to be a matter of common knowledge that many patients with tuberculosis are working when they should be resting. None the less the term "working" seems to me the best estimate of a patient's return to full functional capacity, especially when, as in this series, the greater part of the patients are still under observation and are working with full approval of their physician. Patients still under the cure regimen are listed from our knowledge of their condition as of good or poor prognosis.

REPORT ON 370 CASES IN GROUP 1

The group of patients to be reported in detail constitutes a fair sample of the type of patient generally considered suitable for pneumothorax treatment. Only one case is classified as minimal; 207, or 55.9 per cent, as moderately advanced;

TABLE 2

Age and mortality

AGE GROUP	PER CENT OF GROUP 1 (370)	NUMBER	PER CENT DEAD
Under 20	11.0	41	24.3
20–30	61.6	228	17.9
30–40	17.0	63	15.8
40–50	7.8	29	34.5
Over 50	2.4	9	44.4

and 162, or 43.7 per cent, as far advanced. The ultimate mortality in the moderately advanced group is 13.6 per cent and 29.1 per cent in the far advanced; 174 of the cases are male and 196 female. Collapse was on the right side in 176, on the left in 194 and on both sides in 9 cases. Side and sex exhibit no significant differences in numbers or in mortality.

The effect of age on end-results as expressed by percentage of mortality is studied in table 2. Almost two-thirds of the group fell within the third decade. In the older categories there is a significant rise in mortality only after the age of forty. The second decade has only a slightly higher mortality than those between the ages of twenty and forty.

In table 3 are listed the numbers and mortality rates of those with positive or negative sputum, cavitation or contralateral disease. The comparatively few patients with negative or no expectoration have, as might have been expected, a very low mortality. As regards cavitation in the treated lung as a factor in prognosis, the distinction between the non-cavity and cavity case is sharp. The non-cavity group, constituting less than one-third of the series, has a mortality of only two-fifths of that of the cavity cases. Between the two cavity groups,

under and over 2 cm. in diameter, there is little distinction. In our series, however, there are few of the really gigantic cavities. Slight contralateral lesion within the limits of a minimal rating of the N. T. A. classification has little unfavorable significance as regards prognosis. More than a slight lesion, however, does have a very definite and unfavorable influence.

TABLE 3

Sputum, cavitation and contralateral lesion

SPUTUM	PER CENT OF GROUP 1 (370)	NUMBER	PER CENT DEAD
Positive	81.6	302	23.2
Negative or no expectoration	18.4	68	7.4
CAVITATION			
None	29.4	109	9.2
Under 2 cm. diameter	31.8	118	23.8
Over 2 cm. diameter	38.6	143	25.9
CONTRALATERAL LESION			
None	50.8	188	14.9
Slight	28.8	107	17.8
Moderate	17.2	63	39.4
Moderate and cavity	3.2	12	25.0

TABLE 4

Effectiveness of collapse and mortality

COLLAPSE	PER CENT OF GROUP 1 (370)	NUMBER LIVING	NUMBER DEAD	TOTAL	PER CENT DEAD
Effective	74.7	248	34	282	12.1
Partially effective	21.2	48	31	79	39.3
Non-effective	4.1	6	10	16	62.5
Under 50 per cent	25.0	58	36	94	38.3
Over 50 per cent	75.0	242	41	283	14.5

TABLE 5

Complications

	PER CENT OF GROUP 1 (370)	LIVING	DEAD	TOTAL	PER CENT DEAD
Small or trace effusions	71.0	208	62	270	22.9
Large effusions	29.0	81	29	110	26.4
Empyema	7.1	14	13	27	48.1
Spontaneous pneumothorax	3.9	7	8	15	53.3
Marked symphysis	16.3	46	17	63	26.9
Contralateral spread					
Slight	10.2	34	4	38	10.5
Moderate, improved	4.8	15	3	18	16.6
Severe, progressed	11.0	8	33	41	80.4

A study of what happened to the group of patients during the period of collapse and up to the time of reëxpansion is shown in tables 4 to 7 inclusive.

Probably the most prognostically significant factor in the study is the quality of collapse secured. In table 4, the effective collapse category gives us an important expression of the expectant mortality in well collapsed cases. This was obtained in three-fourths of the group and only 12.1 per cent of these 248 patients have died. The partially effective and non-effective categories offer such striking contrast that our testimony may well corroborate that of many other authors (1, 2) who say that the ineffective collapse should be abandoned after a fair trial and other methods instituted. A study was made of the effective col-

TABLE 6

Duration of pneumothorax and mortality

DURATION	PER CENT OF GROUP 1 (370)	LIVING	DEAD	TOTAL	PER CENT DEAD
Under 1 year	16.9	34	29	63	46.0
1 to 1½ years	7.5	19	9	28	32.1
1½ to 2 years	12.0	34	11	45	24.4
2 to 3 years	22.5	74	10	84	11.9
3 to 4 years	29.3	100	9	109	8.2
4 to 5 years	9.4	29	6	35	17.1
Over 5 years	2.1	7	1	8	12.5

TABLE 7

Status at time of reëxpansion

STATUS	NUMBER	PER CENT
Able to work full-time	162	54.9
Able to work part-time	70	23.7
Curing	63	21.3
Symptom-free	216	73.2
Sputum-negative	243	89.6
Cavity closed	189	96.3

apse group to determine the elapsed time between the institution of pneumothorax and sputum conversion or cavity closure. In 47.5 per cent of these favorable cases the sputum became negative in less than one month. Sputum conversion usually occurred somewhat earlier than the closure of cavity, thus 61 per cent of the sputum-positive cases became negative within three months, and 62 per cent of the cavities were closed within five months. It is worth recording as a point against too early pessimism that in 6 per cent of the cases the cavities remained open during the first year of treatment to be eventually closed; in 11.4 per cent of the cases sputum conversion was similarly delayed. It is probable that most of the delay of sputum conversion was due to contralateral disease.

Other collapse procedures were employed either as an accessory or alternative method. Twenty-four cases or 6.4 per cent of the total cases eventually came to thoracoplasty and about one-sixth of these died. Phrenic interruption was done 38 times with an ultimate mortality of 23.6 per cent. Pneumonolysis was used comparatively infrequently in this series.

Of the complications that may arise in pneumothorax therapy, massive effusion is the most common—29 per cent of cases—and the most serious. One in 4 of our large effusions developed empyema and of these almost one-half died. The total mortality from empyema in the series was 3.5 per cent, and of the 70 deaths definitely due to tuberculosis, empyema was probably responsible for 13, or 18.5 per cent. Spontaneous pneumothorax is listed only 15 times but undoubtedly occurred much more frequently in a slight degree. When a definite diagnosis could be made the mortality is high in this small group, 8 out of 15.

Spread of lesions to the contralateral side occurred in 26 per cent of the series. By far the greater part of these spreads was slight and appeared early in the course of pneumothorax. These lesions were usually in the mid-portion of the lung and appeared to be of bronchogenic origin. However, a good many did occur when no open cavity was noted and in spite of a negative sputum. The slight and moderate lesions were usually handled very well as indicated by a mortality of only 10.5 per cent in the slight, and 16.5 per cent in those listed as moderate. When, however, a serious and progressive lesion developed the story is very different for 4 out of 5 of these cases died.

The cases that were successfully carried through a period of collapse deemed sufficient and that were intentionally terminated show, as might be expected, a very low mortality, 7.3 per cent. Those stopped by nature because of gradually increasing adhesions and obliteration of the pleural space, usually a late complication, also show a low death rate 12.2 per cent; a fact pointed out by Packard (3). Those cases given up as ineffective because of massive effusion or empyema and severe contralateral spread, on the other hand, exhibit a mortality of about 30 per cent.

Table 6 correlates the duration of pneumothorax with the mortality rate. Unfortunately only slight inference can be drawn from this record as to how long pneumothorax should be continued, always a most debatable point in pneumothorax therapy. The cases discontinued in less than two years were stopped almost without exception because they had an ineffective or severely complicated pneumothorax. Naturally the results in this group are poor, especially when the duration is less than one year. The great majority of our cases that were stopped intentionally had had pneumothorax for about three years and their mortality thus coincides fairly closely with that of the group of three to four years duration.

Statistical data bearing on the proper duration of pneumothorax is scanty and difficult to come by as most operators have accepted the dicta of earlier authors that pneumothorax should be continued for from three to five years. Several authors (Packard (3) Aycock and Keller (4)) have expressed the opinion that two years for the average case is the optimum duration. Our recent practice in

pneumothorax has tended this way and I am convinced that somewhat earlier reëxpansion will lead to better anatomical restitution, the avoidance of many complications and equally satisfactory control of the tuberculous lesion.

Table 7 reports the status of the patients at the time pneumothorax was discontinued. One-half of the patients were then back at full-time work and another 23.7 per cent were able to work part-time. About 90 per cent were sputum-negative and 96.3 per cent of the cases who had had a cavity and lived to reëxpand had closed their cavity.

The 75 deaths were studied as regards time of occurrence. Five of these deaths were from conditions other than tuberculosis, but as tuberculosis may have been a factor in their early demise these cases are included. The causes of death of these 5 were: accidental burning, pneumococcal pneumonia in contralateral lung, postoperative pneumonia, coronary thrombosis and cerebral haemorrhage. Of the deaths 22.6 per cent occurred during the collapse period and about 72 per cent of the others occurred within three years of the cessation of pneumothorax. Five patients, however, died after the fifth post-expansion year.

A study was made of the anatomical end-results of the reëxpanded lung based on the X-ray film made after reëxpansion had reached its maximum. The end-results are rated as excellent in 23.5 per cent, this rating meaning a practical return to normal conditions on the affected side; 16.2 per cent show a slight fibrosis or very slight visceral displacement; 32 per cent show moderate deformity of the lung but apparent complete healing of the formerly active lesion; 25 per cent show marked deformity, pachypleuritis or questionable activity or open cavity. Only 8 cases, or 2.9 per cent, are listed as unexpandable. It is probable that a number of those listed as poor should be more properly listed in the unexpandable group, but the distinction in the face of the heavy densities present throughout the lung field is a difficult one to make. While from an anatomical point of view these results cannot be deemed very satisfactory, it has been notable in our series that these cases giving X-ray indication of a badly crippled lung have very little functional disability. Dyspnoea, even of a very moderate degree, is rare and only one case has had any evidence of serious cardiovascular impairment.

Relapse after reëxpansion occurred 35 times, 21 times on the pneumothorax side and 14 times on the contralateral side. A little more than one-half of the 35 occurred within two years of reëxpansion but others occurred from time to time up to ten years.

That these relapses frequently are very serious is evidenced by the fact that 11 deaths occurred in the small series of 35. All of these deaths were in the group of relapse occurring primarily on the pneumothorax side, though in several of the fatal cases extension to both lungs was present.

The final end-results of the series of 370 cases is contrasted in table 8 with the end-results of the 112 cases grouped as unsuccessful. In the unsuccessful group about 50 per cent of the cases were treated with either phrenic interruption, thoracoplasty or both. About two-thirds of the successful group is able to work full-time under normal conditions of living as contrasted with slightly less

than one-third of group 2. One in 5 is dead in group 1, and one in 3 in group 2. Only 2.7 per cent of group 1 are alive but doing badly against 10 per cent in group 2. Of those able to work, 23 have been at full-time jobs for over ten years, 104 for over five years and 186 for over three years.

Pneumothorax is a serious therapeutic procedure but so is tuberculosis a serious disease. Most of the early minimal cases and many of the favorable moderately advanced cases will heal by rest alone. Even an occasional far advanced case which has been denied collapse on account of wide-spread lesion will amaze us by exhibiting the truly miraculous healing power of rest and nature. Statistics of pneumothorax do show an encouraging proportion of cases restored to full working capacity but to the practitioner of pneumothorax the most impressive evidence of its indispensability is still his often repeated experience of being able to check with air collapse the disease that is progressing dangerously in spite of bed-rest.

TABLE 8

Comparison of end-results

Successful and unsuccessful pneumothorax

	SUCCESSFUL		UNSUCCESSFUL	
	Number	Per cent	NUMBER	Per cent
Working full-time	245	66.2	43	38.3
Working part-time	23	6.2	14	12.5
Curing, good prognosis	17	4.6	8	7.1
Curing, poor prognosis	10	2.7	11	10.0
Dead	75	20.3	36	32.1
Total	370	100.	112	100.

SUMMARY AND CONCLUSIONS

Of 770 cases selected for pneumothorax, technical failure of collapse, as evidenced by inability to produce any collapse or a collapse so ineffective that it was abandoned in less than three months, occurred in 157 cases, or in 20.3 per cent. Of these, 60 patients died, a mortality of 38.2 per cent for the category. Of the 770 total cases, 613, or 79.3 per cent, received a technically successful pneumothorax. Of this group, 370 are fully traced throughout the course of their pneumothorax and for an average of five and a half years after pneumothorax was discontinued. Of these, 245, or 66.2 per cent, are able to work full-time, an additional 23, or 6.2 per cent part-time. Twenty-seven patients are still curing and 75, or 20.3 per cent, have died since the institution of collapse.

The most important factors unfavorably influencing end-results are: ineffectiveness of collapse, moderate contralateral lesion at onset, massive effusion and empyema, severe contralateral spread of lesion during collapse, duration of collapse under two years.

At time of reëxpansion, cavity was closed in 96.3 per cent, sputum was negative in 89.6 per cent.

Anatomical end-results in reëxpanded lung were: *excellent* in 23.5 per cent, *very good* in 16.2 per cent, *fair* in 32.0 per cent, *poor* in 25.3 per cent and *non-expandable* in 2.9 per cent.

Relapse in either the pneumothorax or contralateral lung occurred in 35 cases, or in 9.4 per cent of the series. Of these less than one-third died.

The most important unfavorable complication of pneumothorax is the development of a large effusion which occurred in this series in 29 per cent of the cases and in itself appreciably increased the chances of an unfavorable outcome. In this group of large effusions one in 4 developed an empyema and of those almost one-half died. The total mortality from empyema in the series, however, was 3.5 per cent and the incidence in the series 7.1 per cent.

Pneumothorax in spite of its hazards is still a valuable method of treatment for properly selected cases of tuberculosis.

SUMARIO Y CONCLUSIONES

De 770 casos seleccionados para administración del neumotórax, en 157 (20.3%) observóse un fracaso técnico del colapso, traducido por incapacidad para producirlo o ser tan ineficaz que se abandonó en menos de tres meses. De esos enfermos, 60 murieron (38.2%). De los 770 casos, 613 (79.3%) recibieron un neumotórax técnicamente eficaz. De este grupo, a 370 se les siguió durante toda la evolución del neumotórax y por un término medio de cinco años y medio después de abandonarse el último. De ellos, 245 (66.2%) podían trabajar todo el tiempo y otros 23 (6.2%) parte del tiempo, 27 enfermos están todavía en tratamiento y 75 (20.3%) han muerto desde que se les aplicó la colapsoterapia.

Los factores más importantes que afectan desfavorablemente el resultado técnico son: ineficacia del colapso, existencia al principio, de una lesión contralateral moderada, derrame y empiema masivos, propagación contralateral de la lesión durante la colapsoterapia, y duración del colapso de menos de dos años.

En la época de la reexpansión la caverna estaba cerrada en 96.3% y el esputo era negativo en 89.6%.

Los resultados terminales anatómicos en el pulmón reexpandido fueron: *excelentes* en 23.5%; *muy buenos* en 16.2%; *buenos* en 32.0%; *malos* en 25.3% y *faltos de expansión* en 2.9%.

En 35 casos (9.4% de la serie) sobrevinieron recidivas, ya en el pulmón del neumotórax o en el contralateral, muriendo menos de la tercera parte.

La más importante complicación desfavorable del neumotórax es la producción de un derrame grande, lo cual sobrevino en 29% de los casos de la serie y acrecentó en forma apreciable las probabilidades de un desenlace contraproducente. En este grupo de grandes derrames, uno de cada cuatro manifestó empiema y de ellos murieron casi la mitad, pero la mortalidad total debida al empiema en la serie no representó sino 3.5% y las recurrencias 7.1%.

A pesar de los riesgos que entraña, el neumotórax continúa siendo una terapéutica valiosa para los casos de tuberculosis debidamente seleccionados.

REFERENCES

(1) Thompson, L. W., and Janes, R. M.: Collapse therapy in pulmonary tuberculosis, Am. Rev. Tuberc., 1942, *45*, 357.

(2) Jennings, F. L., Mattill, P. M., and Nemic, F. C.: Artificial pneumothorax, Ibid., 1940, *42*, 431.

(3) Packard, E. W.: The present status of one hundred pneumothorax patients after from one to eighteen years expansion of the lung, J. Thoracic Surg., 1932, *1*, 581.

(4) Aycock, G. A., and Keller, P. E.: Voluntary termination of artificial pneumothorax, Am. Rev. Tuberc., 1942, *45*, 117.

AMBULATORY PNEUMOTHORAX[1, 2]

Results of Ten Years' Experience

FREDERICK TICE

It may be well to state, in preface, that the Municipal Tuberculosis Sanitarium has entire charge of the tuberculosis program in Chicago and that the Sanitarium officials must accept responsibility for all phases of tuberculosis work, protective and therapeutic, as well as administrative. In 1931, when the present Board took office, they were faced with both a public health and a housing problem. There were hundreds of patients, most of them open cases, on the waiting lists and for these hundreds, no beds were available and no active measure of therapy was being undertaken. They merely waited, disseminated infection and, in the interim, went from bad to worse.

THE CONJOINED PLAN

To meet the situation, a conjoined plan of field and Sanitarium collapse was instituted. Patients suitable for pneumothorax, for whom no accommodation was available, were started in the dispensary. At the same time, the more or less dormant collapse program at the Sanitarium was steeply augmented. Within the institution, pneumothorax was initiated in every suitable case and the patients, as soon as they had gained a well established collapse, were discharged to the field department for refills. In return, the Sanitarium accepted from the field all patients with indications for institutional care, including accidents, complications and cases calling for additional collapse measures, such as operations on the phrenic nerve, pneumonolysis or thoracoplasty.

The subject assigned to me covers ten years' experience, from July, 1931 to July, 1941. In the time at my disposal and with the statistical help available, it has not been possible to consider every case subjected to ambulatory collapse over this period. A start, however, was made and the survey is still in progress. Altogether and to date, 6,481 charts were closely examined and analyzed. Pneumothorax "attempts" were not considered and all patients listed have had some type or measure of collapse. Of the total number treated, 4,810, or 74 per cent, had ambulant collapse; 2,224 had clinic treatment exclusively; 2,586 combined Sanitarium and clinic care.

THE MATERIAL

As an introduction, it may be said the material dealt with was not promising. Of the 6,500 cases, only 5 per cent were in the minimal stage, 95 per cent were moderately or far advanced; 73 per cent of the cases had positive sputum when treatment was started and 60 per cent showed cavitation.

To explain this volume of apparently unfavorable material, it is only neces-

[1] Presented before the Medical Section at the 38th annual meeting of the National Tuberculosis Association, Philadelphia, Pennsylvania, May 7, 1942.

[2] From the Municipal Tuberculosis Sanitarium, Chicago, Illinois.

sary to recall the latency of the collapse therapy program for the minimal case in former years, the paucity of minimal tuberculosis on the clinic registers and sanatorium admissions and the present wide concept of the collapse indications. Tuberculosis control, for instance, was a factor. Positive sputum, other things being equal, was considered an indication, the "Public Health Indication," as we termed it. This attitude introduced many to collapse who, perhaps ordinarily, would have been considered unsuitable. Every patient who showed bacilli was considered for collapse and the indications were stretched if there was good prospect of conversion.

GROSS RESULTS

Coming to the first summary on results, of the 6,481 cases observed, 60 per cent were living at the time of the report, 25 per cent were dead and 15 per cent could not be traced.

Excluding the patients who died, 21 per cent of the cases showed a gain in weight of 5 to 10 pounds, 20 per cent a gain of 10 to 20 pounds and 15 per cent a gain of 20 pounds and more. In all then, 56 per cent of the patients showed a substantial gain in weight. Thirty-two per cent remained stationary in weight and 12 per cent showed a loss.

Regarding work capacity and excluding non-employables, such as housewives, students and children, 41 per cent of the patients treated with ambulatory pneumothorax were employed at the time of the report. Another 13 per cent were physically employable but, apparently, unable or unwilling to find work. This ratio of work capacity may be considered satisfactory. When expensive and tedious schemes of rehabilitation come up for discussion, it may be well to consider the possibility of ambulant pneumothorax as a rehabilitative measure.

THE UNTRACED GROUP

The figure, 15 per cent, for the untraced may seem high. It is, however, not final. Further research, still in progress, will undoubtedly decrease the percentage. Some of the out-of-town cases will be contacted by mail and many of the city patients, who have moved, will be relocated. We know that none of the missing patients have died within the area of metropolitan Chicago. Our lists have been checked carefully against death reports, not only from the city but from all outlying institutions and none of the cases classed as untraced appear in the death reports.

Meanwhile, in the absence of factual data as to present day condition, the following figures may throw some light on the caliber of the missing patients. At the last examination, 29 per cent of the untraced cases were classed as arrested or apparently arrested, 4 per cent as quiescent, 41 per cent as improved, and 26 per cent as unimproved; 75 per cent had negative sputum.

CLINIC VERSUS INSTITUTION

Needless to say, a period of sanatorium stay for collapse patients is the ideal procedure. Pneumothorax outside the sanatorium is a "second best." Consequently, in terms of efficiency, we would anticipate better results in patients treated in the sanatorium. This anticipation has been borne out. Of the 2,224 cases treated exclusively in the clinics, 53 per cent were living at the time of the report as against 56 per cent for patients receiving treatment exclusively at the Sanitarium. This, however, does not represent the true balance in favor of the Sanitarium. To get this balance we must also analyze the patients who had combined clinic and Sanitarium treatment. Here the margin is wider. Of 1,800 cases receiving both institution and clinic treatment, 73 per cent were living at the time of the report as against 53 per cent living for those who received clinic treatment exclusively.

Crossing initial injection against the place of injection develops a similar trend. Fifty-nine per cent of the 3,400 patients who received initial injections in the clinic were living as against 62 per cent of the 2,200 who had their initial treatment at the Sanitarium.

These comparisons, supported as they are by work in volume, hold several interesting features. In the first place, the margin in favor of the Sanitarium, while appreciable, is not as great as one might have anticipated. In the second place, the necessity of a sanatorium background for a field collapse plan is emphasized by the superior results for patients who had both clinic and sanatorium treatment. In the third place, the necessity of a field background for the sanatorium is even more strongly emphasized. Without clinics to undertake follow-up and refills for ambulant cases, the collapse plan in the sanatorium is definitely out.

PRESENT STATUS OF LIVING CASES

In estimating the present status of living patients, a distinction has been made between patients with reëxpanded and unexpanded lungs. The former cases have been tabulated according to the National Classification. Due to the fact that the lung under collapse does not reveal the true extent of the disease, this classification was not used for patients still under pneumothorax.

Of the 2,800 patients with reëxpanded lungs, 31 per cent are classified as arrested, 20 per cent as apparently arrested, 7 per cent as quiescent, 21 per cent as improved, and 21 per cent as unimproved. Of the 2,000 patients still under collapse treatment, 90 per cent are classed as improved, 10 per cent as unimproved.

INITIAL DIAGNOSIS AGAINST RESULTS

What is the influence of initial diagnosis on end-results? The figures in the series bear out the usual relation in this respect. Taking the entire 5,500 known cases, 96 per cent of the minimal group were living, as against 81 per cent for the moderately advanced and 63 per cent for the far advanced. These results

are gratifying and clearly indicate a more energetic attitude toward collapse of early tuberculosis. The problem centers on the discovery of the minimal case. At the present time, through the medium of a total X-ray survey in the congested areas, we are attempting to discover as much early tuberculosis as possible and apply collapse treatment.

AGE, RACE AND SEX

The present study bears out our previous observation that the Negro, according to all appearances, does not adapt to collapse treatment quite as well as the white. This holds good for both the purely ambulatory cases and the cases who had had Sanitarium care. Taking white cases treated, 62.5 per cent were living as against 50 per cent of the Negroes. This disparity of 25 per cent has held constant in previous studies. Appearances, however, may be deceitful. It must be recalled that, in Chicago, the Negro-white mortality ratio is six to one and that, in the collapse cases, this ratio has been very much decreased.

Regarding age, the figures, as might be expected, show a somewhat higher mortality in the very young and very old, with best results in the twenty to thirty-five year group. At the time of the report, 32 per cent of the children under fifteen were dead, 35 per cent of the patients over fifty, and only 22 per cent of the patients in the twenty to thirty-five year period.

As to sex, while the figures showed slightly better results for the females, the tabulations otherwise were uninteresting.

SPUTUM CONVERSIONS

The sputum is held converted when (three months after the last positive) three specimens taken one week apart are negative and continue negative thereafter. The concentration method is used and culture, guinea pig inoculation and examinations of gastric contents are done as indicated.

Of the 3,400 living cases that had had positive sputum, 73 per cent were converted; 77 per cent of 390 patients treated by thoracoplasty, 74 per cent of 2,000 treated by pneumothorax, 73 per cent of those treated by pneumothorax and phrenic combined and 61 per cent of 171 treated by phrenic operations alone were converted.

Thirty-four per cent of the cases were converted in less than three months, 19 per cent between three and six months, 47 per cent in six months and over. The time interval was estimated from the date of the primary operation, whether pneumothorax, phrenic or thoracoplasty.

The change in sputum status was not merely transitory; 1,137 of the cases remained persistently negative and were still negative three years and over after conversion, 358 were still negative two to three years after conversion, 463 one to two years, and 512 recently converted cases showed continuously negative sputa at the time of the report.

Balancing the conversion rate for the ambulant cases against the rate for patients who had Sanitarium treatment, the figures ran 64 per cent conversion for the clinic alone, 80 per cent for combined clinic and Sanitarium treatment,

and 73 per cent conversion for those who had treatment exclusively in the Sanitarium. In other words, as one might suppose, the rates ran parallel to those already given for survival. Here, again, the figures for patients who had combined Sanitarium and clinic treatment were best.

CAVITY CLOSURE

In view of mechanical considerations and pathological sequence, sputum conversion and cavity closure should, more or less, go hand in hand. Such has been the experience in this present report. Of the 2,711 living cases that had had cavitation, 2,044, or 75 per cent, showed complete closure, 179, or 7 per cent, incomplete closure and 488, or 18 per cent, remained stationary or showed extension. Here, again, the figures ran best for those who had combined Sanitarium and clinic treatment.

TYPE OF TREATMENT AGAINST RESULTS

Considering all cases studied, of the 6,481 patients, 5,600 had pneumothorax with or without ancillary measures, 1,600 patients had a phrenic operation, 191 had pneumolysis, 490 had thoracoplasty, 237 had pneumoperitoneum, 187 oleothorax and 89 extrapleural pneumothorax.

The number of pneumonolysis operations, 191, the equivalent of 3.4 per cent of the pneumothorax cases, seems small in comparison with other reports. Most workers feel that between 10 and 20 per cent of established pneumothorax cases are apt to need this type of surgery somewhere along the course.

With regard to outcome, thoracoplasty, in combination with other procedures, gave the best results, 74 per cent living against 60 per cent living for pneumothorax alone, 56 per cent for pneumothorax and phrenic combined, and 45 per cent for phrenic alone. These results in favor of thoracoplasty run counter to the older conception and indicate for us the future scope of this operation.

During the last ten years, in the Municipal Tuberculosis Sanitarium, close to 700 patients have had thoracoplasty, practically all operated by our Secretary of the Board of Directors and chest surgeon, Dr. Richard Davison. Timely intervention probably has had much to do with the success of the procedure.

RESULTS AGAINST YEARS

A correct correlation between results and lapse of time since start of treatment is difficult. In metropolitan centers the number of "untraced" increases with the years. Many of the cases dismissed from active clinic supervision as arrested, fail to return for the semi-annual check-up. Many others, as they improve, objecting to the nurse's call and anxious to escape supervision, take the matter into their own hands and dismiss themselves. As a consequence of this regrettable trend, a third of the 257 cases treated in 1931 had not recently been observed. Even including these "untraced" in the total figures, 34 per cent of the patients treated in 1931 were living ten years later. As already mentioned, 74 per cent of these untraced cases were in the better classifications at the time of last contact and 75 per cent had negative sputum.

It is, therefore, perhaps justifiable to assume that the survival rate of the untraced cases was at least as good as for the total known cases. Figuring on this assumption, 51 per cent of the patients treated in 1931 were still living ten years later. On the same basis, 63 per cent of the 721 cases treated in 1936 were living five years later, 74 per cent of the 728 patients started in 1938 were living three years later and 88 per cent of the 743 cases started in 1940 were living a year later. From 1938 on, the number of untraced cases was small, running from 11 per cent in 1938 to 4 per cent in 1940. On the whole and in comparison with the well known picture of open tuberculosis, the results balanced against the time element may be considered satisfactory.

CONCLUSIONS

Since 1931, the officials of the Municipal Tuberculosis Sanitarium have advocated large scale field collapse, both as a public health instrument and as a measure beneficial to the individual patient. In advocating this policy in 1931, we said, in a Bulletin of that year: "We can turn off the fountains of infection more expeditiously, more thoroughly by compressing a diseased lung than by isolating a patient."

We still hold this belief and adhere to this policy. At the present time, close to 2,000 ambulant patients are receiving treatment in the clinics and the number is growing daily. Notwithstanding consistent opposition in certain quarters, resistance to the concept of field pneumothorax in massive application is disappearing and indications point to increasing use of the measure for metropolitan centres.

SUMMARY

Over a period of ten years, 6,481 patients were treated with collapse, 34 per cent while ambulant all the way through the collapse treatment, 40 per cent with combined Sanitarium and clinic management and 26 per cent with Sanitarium management alone.

The patients dealt with were prognostically unpromising, 95 per cent being moderately and far advanced and 73 per cent had positive sputum.

The results of Sanitarium treatment were better than those of clinic treatment and the results of combined clinic and Sanitarium treatment were best.

Negro patients did not respond as well as white but the difference in the collapse group was considerably less than that in the official tuberculosis mortality.

Both from the point of view of survival and of sputum conversion, thoracoplasty outranked the other measures in efficacy.

SUMARIO

En un período de diez años, 6,481 enfermos recibieron la colapsoterapia: 34% de ellos mientras continuaban en estado ambulante durante el tratamiento, 40% con asistencia combinada en el Sanatorio y la clínica y 26% exclusivamente con trataminento sanatorial.

En ninguno de estos enfermos era el pronóstico halagüeño, siendo 95% moderados o muy avanzados y teniendo 73% esputo positivo.

El resultado del tratamiento en el sanatorio fué mejor que en la clínica, pero la combinación del tratamiento en la clínica y el sanatorio fué lo que dió mejor resultado.

Los enfermos negros no respondieron tan bien como los blancos, pero en el grupo que recibió la colapsoterapia, la diferencia entre ambos grupos fué considerablemente menor que en las tablas oficiales de mortalidad tuberculosa.

Tanto desde el punto de vista de la sobrevivencia como de la conversión del esputo, la toracoplastia superó a todos los demás métodos en eficacia.

EXTRAPLEURAL PNEUMOTHORAX[1, 2]

Late Results

PAUL GEARY

It was during 1938–1939 that extrapleural pneumothorax was done most frequently. Since that time, it has been distinctly less in favor and subjected to adverse criticism which in a large measure is justifiable. This report deals with the results of 75 patients, most of whom were operated upon in the 1938–1939 period. The average time since operation for the whole group is slightly over forty months.

When we adopted the operation, we thought that it could be used much the same as intrapleural pneumothorax in cases where thoracoplasty was not thought wise and intrapleural pneumothorax was not possible because of adherent pleura. It was expected that the lung would remain collapsed until the lesion had presumably healed and could then be reëxpanded. This reasoning would presuppose that there was enough healthy parenchymal tissue in the lobe adjacent to the disease and in the lower and middle lobes to allow expansion to occur and that the dense fibrous capsule created by the extrapleural air would be elastic enough to allow the lung to expand under it. There is undoubtedly a tendency of the underlying lung to expand, but we have noted in our 18 patients who are alive at this time with abandoned extrapleural pneumothorax that the extrapleural thickening resists expansion of underlying tissue and much of the defect in the chest made by the operation is closed by retraction of the mediastinum and compensatory emphysema of the contralateral lung, as well as by a drawing upward of the ipsolateral lung rather than by its reëxpansion. This is true particularly in cases in which the space had been established for a relatively long period. In certain cases where the extrapleural pneumothorax space had to be abandoned early there was complete expansion. In intrapleural pneumothorax a lung which has been destroyed by tuberculosis will not expand after a period of three to four years because there is no healthy elastic tissue present, while a lung with little disease and much elastic tissue can be kept collapsed only with frequent refills. Of course, the fibrous extrapleural capsule is more dense than the pleural thickening seen in intrapleural pneumothorax. We have observed a dead space of extrapleural pneumothorax which had no tendency to obliterate one year after pneumothorax was discontinued. Thoracoplasty has recently been done on this patient. Our belief is that extrapleural pneumothorax after its establishment has more of a tendency to cause permanent restriction in the size and mobility of the lung than intrapleural pneumothorax and in most cases cannot be considered a reversible method of treatment.

[1] Presented before the Medical Section at the 38th annual meeting of the National Tuberculosis Association, Philadelphia, Pennsylvania, May 7, 1942.

[2] A late report on operations performed at the New Jersey State Sanatorium, Glen Gardner, New Jersey; Bonnie Burn Sanatorium, Scotch Plains, New Jersey; and the Roosevelt Hospital, Metuchen, New Jersey.

We have had only 2 patients whose extrapleural pneumothorax was abandoned intentionally because the maximum therapeutic effect had been reached. The period of treatment was thirty-seven months in the first patient and thirteen months in the second.

Following abandonment of the pneumothorax, we have observed the spaces for nine and thirty months, respectively, and found that the operative region gradually becomes opaque in the X-ray picture and retraction of the tissues occurs, but there is no evidence that the pulmonary tissue reëxpands.

Ten of our patients, including 2 children, were good risks with active disease on only one side confined to the upper lobe, with cavities of less than 5 cm. in diameter, who would have been acceptable for thoracoplasty.

Twenty-three patients, mostly good operative risks, were selected for the following reasons: basal cavitation, to convert an inadequate intrapleural pneumothorax to a combination extra- and intrapleural pneumothorax, haemorrhage and bilateral disease where the contralateral disease was controlled by pneumothorax or some other form of compression therapy. To-day we would prefer thoracoplasty in many patients of this group.

The other 42 patients were the poorest risks with unfavorable prognoses. Included were the toxaemic patients with cavitation and progressive disease, those who had bilateral cavitation with inadequate or no contralateral collapse and those in whom age, systemic disease or other factors made them unsuitable for thoracoplasty. To-day we would refuse operation in many of this group, in others it would be deferred until a more auspicious time and others would be selected for thoracoplasty.

It is true that many of our patients were not considered to be in satisfactory condition for operation, nevertheless, we have not experienced a low operative mortality and feel that in poor-risk patients there is considerable danger from the operation. It has also been stated that after induction of an extrapleural space, subsequent thoracoplasty is less dangerous than usual. We do not agree with this statement and feel that there is more danger than in the uncomplicated first-stage thoracoplasty.

The very thought of extrapleural pneumothorax discourages many thoracic surgeons for two very simple and sound reasons. In the first place, the surgeon recalls all the complications he has had with his own patients and others he has heard of from his colleagues. Second, in the patients who escape early complications, in whom the space is established, the disease controlled and regular refills being given, there is still the feeling of insecurity about the space itself which should be considered a temporary expedient that requires obliteration by thoracoplasty or oleothorax at a future time.

The complications of the operation are many but by far the most distressing of all is the vulnerability of the space to infection. This complication, as noted by other authors, does not necessarily occur early and is sometimes not manifest until a year later.

We have used rigid standards in determining whether or not infection is present in the space.

We consider the space infected in the presence of purulent material from which no organism can be obtained, in the presence of either cloudy or clear fluid containing organisms, and last, in cases where seropurulent fluid persists though no organisms can be recovered.

By these standards, we have had the high number of 28 infections in a series of 75 patients, or in 37.3 per cent. Twenty-two were tuberculous, 2 were caused by *Staphylococcus aureus* and 4 were mixed infections. One staphylococcus infection occurred during the first month, the other six months after operation. Tuberculous and mixed infection usually took place between the third and ninth month. Though many of these infections cleared up under treatment, in other patients the space was abandoned because of the infection and in others it was converted to oleothorax. Such a high incidence of infection is a great hazard, and we should all think twice before subjecting a patient to such danger. This incidence of infection is not the highest recorded. In a recent report of 30 cases, Thompson and Janes found one pyogenic infection, 8 early tuberculous infections and 3 late tuberculous infections, which is a total of 40 per cent.

At the time of our first report in 1939, we had had no demonstrable broncho-extrapleural or extrapleural-cutaneous fistula. Since then, 3 extrapleural-cutaneous fistulae have developed, 2 by infection of needle tracts in the course of irrigating an infected space and one at the site where a chest wall abscess, connecting with the space, pointed anteriorly. One patient is dead, another healed after expansion of the lung and the third is healed except for a small sinus after obliteration of the space by thoracoplasty.

In each infected case, an attempt was made to demonstrate a broncho-extrapleural fistula with methylene blue. The dye which was injected into the space was subsequently expectorated by only 2 patients; a smaller incidence of bronchial fistula than would be expected. Each of the patients had extensive contralateral lesions and subsequently died.

We observed reëxpansion of the lung at all stages in the postoperative period. Some spaces have been abandoned within a few days after operation when it became obvious that there was not enough pulmonary reserve to sustain life, for example in a patient who had a contralateral thoracoplasty. In another patient, the presence of contralateral pneumothorax made it impossible for the patient to survive with the second lung collapsed by extrapleural pneumothorax. It has often been our observation that the greatest factor in spontaneous obliteration of an adequately dissected extrapleural pneumothorax space is the lack of functioning pulmonary tissue. This shortage of functioning pulmonary tissue is due in some cases to contralateral collapse therapy and in others to destruction of pulmonary tissue by disease. Where this condition exists, it is obviously unwise to substitute oil for the air to prevent the expansion of the lung because a comparable amount of dyspnoea will be present if the compression is continued with oil.

Many of our cases of tuberculous empyema would not respond to local treatment and were cured by allowing the diseased lung to reëxpand.

Where adequate pulmonary reserve was present, maintenance of the space

during the first six-months period was easy. We have not experienced sudden early expansion. With a few exceptions where the space could not be properly developed because of adhesions and in one other early case where the dissection was too limited, we have been satisfied with the technical development of the space.

Two extrapleural spaces were abandoned because the disease was not controlled by the operation. In another case, contralateral pneumothorax had to be discontinued because of dyspnoea. This was followed by activation of contralateral disease which had previously been controlled. Another space was abandoned because of persistent spontaneous pneumothorax on the operative side.

We have had trouble with postoperative haemorrhage into the space in only 2 patients. One was controlled by transfusion, aspiration and irrigation. The result was satisfactory. In the other patient, who had much less bleeding, the development of the space was always inadequate. The pneumothorax was discontinued as ineffectual after six months.

Twenty-two of our patients are dead. Six deaths occurred within the first three months after the operation and are listed as operative deaths. The causes were as follows:

Postoperative spread	2
Toxaemia and exhaustion	1
Acute tuberculinization	1
Blood stream infection (Str. viridans)	1
Circulatory failure	1

Among patients who later were treated by thoracoplasty, 2 died in the postoperative period, one from cerebral embolism and the other from circulatory failure. Eleven died from progression of the disease. One died of ruptured appendix with peritonitis, one of a late cardiac complication and another of lobar pneumonia two and a half years after operation.

Excluding the patients who died following thoracoplasty, the operative death rate would be 8 per cent, which is high, and does not bear out the contention that the operation is innocuous and less dangerous than thoracoplasty.

In addition, we feel that conditions exist after an unsuccessful extrapleural pneumothorax which make a thoracoplasty less likely to succeed than a primary thoracoplasty. Among these factors may be mentioned the rigidity and density of the tissues caused by the extrapleural pneumothorax and the fact that in these patients more incapacitating disease is usually present.

Among our own patients, 2 who had thoracoplasty were completely successful, one is doing well after a recent operation, 2 died from the operation, one continued to progress in spite of the operation, one has had an anterior draining sinus for over a year but is clinically well with negative sputum. Another had the first stage of thoracoplasty nine months ago. Amyloid disease and other complications have made it imprudent to continue the operation.

As mentioned above, 18 patients are alive with reëxpanded lungs or, to speak

more accurately, the extrapleural pneumothorax space has been abandoned in them. In 2, the abandonment of the pneumothorax was elective because it was thought that the underlying pulmonary disease had healed. Eleven of the patients in this group are quiescent with negative sputum. How much credit belongs to the extrapleural pneumothorax for bringing about this improvement in the patient's status is questionable. Undoubtedly, it has helped some, but the procedure was involuntarily abandoned before the maximum therapeutic effect had been considered achieved.

Present Disposition of Cases

Space maintained, regular refills	27
Alive with reëxpansion	18
Alive with thoracoplasty	5
Alive with oleothorax	4
Dead	22
Total	76*

* One patient has oleothorax on one side and thoracoplasty on the other.

We have had considerable experience with paraffin plomb and are familiar with the late complications, such as erosion of the plomb into diseased pulmonary tissue with infection of the space and expectoration of the paraffin. Fistula into an oleothorax space has its own unpleasant effects, such as contralateral dissemination of the disease, which are well known to those who use it in intrapleural therapy. With these thoughts in mind, we have been reluctant to change our air spaces into oleothoraces.

Oleothorax

(For infection of space)

1. A. L.—Made worse by oleothorax and had thoracoplasty later.
2. H. C.—Filled with fluid so rapidly that oil could not be handled and had thoracoplasty later.
3. M. S.—Was not helped by oil. Progressive expansion continued. Also had thoracoplasty later.
4. C. W.—Severe reaction to oil and had thoracoplasty later.
5. E. N.—Satisfactory to date.
6. L. M.—Satisfactory to date.
7. J. J.—Satisfactory to date.
8. M. P.—Satisfactory to date.

Thirty-seven, or 49 per cent, of the entire group are quiescent with negative sputum. The results in women have been much superior to those in men. Out of 54 females operated upon, 33, or 61 per cent, have negative sputum and are quiescent, while only 4, or 19 per cent, of 21 males have negative sputum and are quiescent. This apparent discrepancy could partially be accounted for by differences in age and nature of the pulmonary disease.

In contrast to thoracoplasty where convalescence from the operation often marks the end of the patient's discomfort and worry, the extrapleural pneumo-

thorax operation is the beginning of a prolonged period of apprehension for both patient and physician. We must consider the inconvenience to the patient of refills, the danger of bronchial fistula and infection, premature expansion of the lung, and last the possibility of eventually having to face thoracoplasty.

Our opinion to-day is that the great majority of patients who can stand the operation of extrapleural pneumothorax can stand a thoracoplasty; that it is often poor judgment to do the operation on a patient with an extensive bilateral lesion. It is frequently said that these patients will surely die without the operation. That is true, but it is better for them to die without the mental and physical discomfort of surgery in their last days.

It is hard to state concretely our indications for the operation. At this time, we believe it should be done in all children in preference to thoracoplasty. Especially, selected cases with haemorrhage, for instance, may be benefited until the patient is more stable and in condition for multiple-stage thoracoplasty. We feel that other indications do not belong in categories and call for careful evaluation of each patient, as to ability to tolerate the operation and subsequent thoracoplasty, or to go along with extrapleural pneumothorax or possibly oleothorax indefinitely.

The operation of extrapleural pneumothorax is dangerous, as are the many complications of the operation. When it is successful, we are faced with the problem of disposing of the space. Proctor believes all spaces should be converted to oleothorax; Dolly and his associates have reached the same conclusion after careful study of the problem. We are not sure that oleothorax is the last word and conclude that the extrapleural pneumothorax procedure is unsatisfactory and should be used infrequently.

SUMMARY

An extrapleural pneumothorax space was established by operation in 75 patients whose average postoperative period is slightly over forty months. The early results were reasonably good, but as the postoperative period increased so also did the complications.

Infection of the space, which often developed late, was present in 37.3 per cent of the patients and was the most serious complication.

The operation is considered as dangerous as thoracoplasty, while the obliteration of an unsatisfactory extrapleural pneumothorax space by thoracoplasty is more dangerous at times than the thoracoplasty as first operation.

The space was abandoned in only 2 patients because the pneumothorax was no longer thought necessary.

There is little tendency toward reëxpansion in a lung that has been collapsed by prolonged extrapleural pneumothorax.

Routine conversion of the pneumothorax spaces into oleothorax has not been adopted.

Because of operative risk, frequency of complications and uncertain end-results, extrapleural pneumothorax is unsatisfactory.

SUMARIO

Aparentemente se estableció un espacio neumotorácico extrapleural en 75 enfermos cuya evolución postoperatoria promedió poco más de 40 meses. Los resultados tempranos fueron razonablemente buenos, pero al ir avanzando el período postoperatorio, también aumentaron las complicaciones.

En 37.3% de los enfermos se presentó a menudo tardíamente infección del espacio, siendo ésta la complicación más grave.

Debe considerarse esta operación tan peligrosa como la toracoplastia, mientras que la conversión de un espacio neumotorácico extrapleural no satisfactorio en una toracoplastia resulta a veces más peligrosa que la toracoplastia primaria.

Sólo en dos enfermos se abandonó el espacio por no considerarse ya necesario el neumotórax.

Obsérvase poca tendencia a la reexpansión en un pulmón aplastado por un neumotórax extrapleural prolongado.

No se ha adoptado la conversión sistemática de los espacios neumotorácicos en oleotórax.

Debido al riesgo operatorio, a las frecuentes complicaciones e incertidumbre de los resultados terminales, el neumotórax extrapleural resulta poco satisfactorio.

REFERENCES

(1) Dolley, Frank S., Jones, John C., and Skillen, Jane: Extrapleural pneumothorax, Am. Rev. Tuberc., 1940, *41*, 403.
(2) Geary, Paul: Extrapleural pneumothorax, Ibid., 1939, *40*, 9.
(3) Proctor, O. S.: Extrapleural pneumothorax and oleothorax, J. Thoracic Surgery, 1940, *9*, 392.
(4) Thompson, L. W., and James, Robert M.: Collapse therapy in pulmonary tuberculosis, Am. Rev. Tuberc., 1942, *45*, 357.

DISCUSSION

Dr. Eli H. Rubin, New York: In the earlier years of pneumothorax treatment of pulmonary tuberculosis, disease in the contralateral lung was considered a contraindication to the collapsing of the more actively diseased lung. This was based on the belief, never proven, that the untreated lung would be overworked, which might aggravate any latent disease present. Later, when it was noted that therapeutic pneumothorax was occasionally associated with improvement in complicating tuberculous laryngitis, that nephrectomy for tuberculous kidney was occasionally followed by improvement of tuberculosis in the urinary bladder, opinion swung to the other extreme; contralateral disease was considered an added indication for treatment.

The truth of the matter probably lies in the observations made by Drs. Jennings and Mattill (Am. Tuberc., 1942, *45*, 461). Pneumothorax treatment neither improves nor aggravates latent disease in the untreated lung. Individuals in whom serial X-ray films prior to pneumothorax induction show improvement in the disease in the contralateral lung continue to do well. Patients in whom previous films show unstable or progressive disease in the untreated lung get worse. Since one is usually dealing with a stationary

process, the contralateral lung in most instances shows no change. The effect of a satisfactory pneumothorax on the untreated lung is to minimize the danger of intracanalicular spread.

The end-results reported by Doctor Morriss from pneumothorax treatment of pulmonary tuberculosis, about two-thirds able to work, 96 per cent cavity closure, 90 per cent negative sputum, are considerably better than the average results obtained in collected statistics. Judged by acceptable standards, end-results range about 40 per cent cured or fit. I am referring to results obtained before the wide-spread application of adhesion cutting. Doctor Morriss could tell us better the factors which he thinks contributed to the exceptionally good results at the Gaylord Farm Sanatorium. My impression is that he will find the answer in the title of his paper: selection for pneumothorax. There are very few reports that give such a high percentage of intentionally discontinued pneumothoraces. This is a good gauge of the type of treatment given at the Gaylord Farm Sanatorium. As to his observations on the effects of larger effusions on pneumothorax, I agree with him that, although statistics may show little difference between dry and wet cases and individual patients may even find an intercurrent effusion a providential event, on the whole, effusions complicate the treatment, cause premature loss of pleural space and often expose the patient to the danger of empyema. Patients are better off without effusions.

The results reported by Doctor Tice with ambulatory pneumothorax treatment in several thousand cases indicate that the application of the treatment is feasible on a large scale. In New York City, instead of concentrating the work in one clinic, the treatment is given under unified direction in eleven clinics connected with city hospitals. There is some advantage in treating patients near their homes. There are many advantages in having the clinics within hospitals. I don't have time to go into further aspects of the subject.

At the present, approximately 2,100 patients are receiving 37,000 refills a year in New York City. The results that are being obtained are probably the same as in Chicago, depending primarily on the character of the collapse established before ambulatory treatment is undertaken. I do not favor induction of pneumothorax in a clinic. No statistical data will change my opinion.

Doctor Geary's conclusions that extrapleural pneumothorax presents a combination of hazards which weigh heavily against its benefits express the views of most physicians. At Montefiore Hospital we have had much less experience with the method, having applied it in only 7 cases. Our experience has been the same. The advisability of using extrapleural pneumothorax is often discussed. We usually decide to enlarge the indications for thoracoplasty.

Dr. Jane Skillen, Olive View, California: During the past five years extrapleural pneumothorax has had extensive application, both in this country and abroad. Doctor Geary's later results in the cases which he presented three years ago are significant in the evaluation of this procedure. His article on extrapleural pneumothorax in the American Review of Tuberculosis, July, 1939, was more enthusiastic than at present, but the results he presented then, as now, can be matched in the experience of others.

That extrapleural pneumothorax is not a panacea for all forms of tuberculosis was early recognized by its proponents. Attempts to delimit its indications have been repeatedly made. The absolute indication as laid down by Schmidt, recent limited unilateral cavities in patients otherwise in good condition, undoubtedly yield the best results with this

form of treatment, but even better results might be expected in many of these cases if treated with thoracoplasty. Cases with contralateral cavities, poor physical condition, where thoracoplasty seems to be contraindicated, have given less encouraging results, but are often doomed without this procedure, and it is in this group that the extrapleural operation may have, in the end, its greatest application. In children also it offers obvious advantages. Early conversion to oleothorax when space is being lost or when infection develops has saved many of our cases and should not be rejected because of theoretical objections. Attempts to use materials other than air or oil are still being made and may offer advantages, in some cases.

The report given by Doctor Churchill at the annual meeting of the National Tuberculosis Association last year may be supplemented now with the further experience of the 150 extrapleural pneumothorax cases at Olive View, during the past five years.

The early results in cases more recently instituted still seem as good as in California groups previously reported, and better than has been reported by many American surgeons in other places.

The frequency of complications, empyema and fistulae, and of the replacement of air by oil in the three successive sets of 50 cases has been quite similar.

The late results are less gratifying. Many of our earlier patients are apparently cured, and working, and many others have continued to have negative sputum and cavity closure, but a number have reopened their cavities and again show positive sputum, and in about a score the extrapleural space had to be discontinued because of failure of cavity closure, adhesions, etc.

Extrapleural pneumothorax appears to us to be about as effective as intrapleural pneumothorax and complications are also frequently encountered. Its adequate establishment and postoperative management are much more arduous and difficult. In cases where intrapleural pneumothorax cannot be established and thoracoplasty is contraindicated, it fills a gap in phthisiotherapy that should not be disregarded.

Dr. John W. Towey, Powers, Michigan: In the time allotted to me for discussion I would like to direct my remarks to the subject presented by Doctor Tice. I might take issue with certain medical phases of his program but it intrigues me with its economic possibilities. In discussing this paper I wish to single out pneumothorax therapy, without any entanglements as regards other collapse measures.

The ambulatory pneumothorax program as outlined would be definitely influenced by environmental factors. Doctor Tice and his associates are dealing with patients in a metropolitan area where distances and means of transportation are minor factors. Our institution in Michigan is located in a rural section. There the transportation of patients becomes a major problem in this type of program. We have approximately 50 ambulatory patients reporting to the sanatorium for refills. These patients travel distances ranging from a few miles to 150 miles. The present tire situation merely emphasizes a problem which had previously existed. Where the patient is having refills at short intervals or where the condition of the patient is such that travelling is a hardship, then hospitalization does not become a matter of choice but one of necessity.

Sufficient beds to isolate infectious cases of tuberculosis is a basic provision in any sound tuberculosis program. Except in dire emergencies it has been our policy never to institute pneumothorax without the patient's being hospitalized. A large percentage of cases in which pneumothorax is instituted would be classified as communicable and will most often remain so until a satisfactory collapse renders them noncommunicable. We

feel that a short period of treatment in a sanatorium is better than none, both from the standpoint of results obtained and from the standpoint of the education of the patient as regards the future management of his disease. This short period of hospitalization permits the attending physician to make a more thorough clinical study of the individual.

Pneumothorax instituted and continued without previous hospitalization may serve a purpose in communities of relatively low economic status with high mortality rates, but it is still a compromise with modern public health thought and should be recognized as such.

The ambulatory pneumothorax patient should be one whose disease has been rendered noncommunicable. He should be symptom-free and his collapse should be well under control. The proportion of such patients will be in direct proportion to the stage of their disease when treatment is instituted. As a general rule the earlier the lesion, the more satisfactory is the collapse and the shorter is the period of hospitalization. This program merely emphasizes the importance of early diagnosis. Early diagnosis plus prompt and adequate collapse therapy offers vast possibilities for a comparatively rapid turn-over of our hospital population.

Photo-roentgenographic technique has solved the problem of X-ray costs. At the present time a large number of these units are being used in the selection of men for our armed forces. It is reasonable to expect that at the end of the duration a large proportion of these units will be brought into civilian use. In addition a large number of men are being trained, during service who later will be available for case-finding activities.

PNEUMOTHORAX CASES TREATED AT A CLINIC[1]

D. R. HASTINGS AND BORGHILD BEHN

During the ten-year period from January, 1930 through December, 1939, over 500 patients were discharged from Glen Lake Sanatorium with pneumothorax established more or less satisfactorily. Approximately half of these patients reported to their private physicians for continued treatments, while the rest were cared for at the pneumothorax clinic under the supervision of the Glen Lake Out-Patient Department. In all, there were 245 individuals who reported to the clinic at some time during this ten-year period. Although this series is perhaps not extensive enough for any detailed statistical analysis, it should provide some indication as to the progress of pneumothorax patients who report to clinic for treatment after their discharge from the sanatorium.

We wish also to determine how the progress of these pneumothorax clinic patients compares with that of other groups of patients after their discharge from the sanatorium. For comparison with these 245 pneumothorax clinic cases we have the records of 680 ex-patients who have attended the other clinics under the supervision of the Out-Patient Department during the same ten-year period. We also have the records of 2,776 ex-patients who were alive at the beginning of the ten-year period under consideration, and who did not report to any clinic after their discharge from the sanatorium. Only those patients discharged after January, 1926 are included. The Glen Lake Out-Patient Department was not established until the summer of 1925, and records prior to January, 1926 are too incomplete to be of value for this study.

The information concerning the clinic patients has been obtained from the clinic records, supplemented by data from the patient's correspondence chart and discharge summary. The data from the various sources were assembled and recorded on specially designed punch cards for all clinic patients. The information concerning patients who did not report to any of the clinics after discharge from the Sanatorium was obtained from their discharge summaries, and is naturally much less complete than the data for clinic patients. These discharge summaries, which include all follow-up information concerning the patients, are also recorded on punch cards.

DISCUSSION

The development of fluid within the pneumothorax cavity is probably the most common of all complications of artificial pneumothorax. Table 1 gives the percentages developing fluid and empyema after discharge from the sanatorium among these 245 clinic cases, classified according to stage of disease on discharge from the Sanatorium.

The percentage of pneumothorax cases developing fluid at some time during the course of treatment, as reported by various investigators, ranges all the

[1] From the Glen Lake Sanatorium Out-Patient Department, Minneapolis, Minnesota.

way from 29 to 90 per cent. It is likely that this wide divergence in percentages reported is due in part to differences in the type of cases treated by artificial pneumothorax and in part to variations in criteria for determining the presence of fluid. For instance, Diamond and Ivey (3) found that over 85 per cent of their cases showed some evidence of fluid, but that appreciable amounts of fluid were present in only 40 per cent of the cases, and that empyema developed in 10 per cent of their cases. Jennings and Mattill (5) found that fluid occurred in appreciable amounts in 53.5 per cent of the cases treated at Glen Lake Sanatorium, while 15.3 per cent of these cases developed empyema. Among the 245 cases considered here, the percentage showing evidence of fluid, as well as the percentage developing empyema, while they were receiving their treatments at clinic, are perhaps a little below the average of the percentages reported in the literature. Apparently the complication of fluid occurs no more frequently among individuals receiving their treatments at clinic than among any other group of pneumothorax cases.

Myers (9) found in his study of 239 ambulatory pneumothorax cases that empyema developed in 3 per cent of the minimal, in 5 per cent of the moderately advanced and in 15 per cent of the far advanced cases. There is considerable other evidence in the literature on pneumothorax to indicate that, in general, empyema is much more likely to develop in those patients whose tuberculosis was far advanced than among those whose tuberculosis was moderately advanced or minimal at the time pneumothorax was established. The percentage of cases developing empyema among the minimal, moderately advanced and far advanced cases in this group of 245 pneumothorax clinic patients seems to be about the same as those reported by other investigators. There seems to be little question that empyema is more likely to prove a complication of artificial pneumothorax among the far advanced cases than if the patient's tuberculosis was in the minimal or moderately advanced stage at the time pneumothorax was established.

TABLE 1

	NUMBER OF CASES	NUMBER AND PER CENT DEVELOPING FLUID	NUMBER AND PER CENT DEVELOPING EMPYEMA	PER CENT OF TOTAL DEVELOPING EMPYEMA
Far advanced	143	79 (55.2)	12 (15.2)	8.4
Moderately advanced	90	55 (61.1)	2 (3.6)	2.2
Minimal	12	9 (75.0)	0 (0.0)	0.0
Total	245	143 (58.4)	14 (9.8)	5.7

The condition of the patient at the time of his discharge from the Sanatorium, for this series at least, apparently bears no relationship to the incidence of fluid which may develop subsequently. Of the 153 cases that were classified as arrested or apparently arrested on discharge, 89, or 58.1 per cent, developed fluid, while 54, or 58.7 per cent, of the 92 cases classified as quiescent, improved or

unimproved, showed evidence of fluid. However, only 2.6 per cent of those classified as arrested on discharge from the Sanatorium developed empyema, while 10.9 per cent of those who could not be so classified developed empyema. Even though the number of cases is not very large, the difference between these two percentages is statistically significant. The ratio of this difference to its standard error is 2.68, and the odds against a difference of such a magnitude being due to chance alone are approximately 135 to one. It seems fairly clear on the basis of these figures that patients whose tuberculosis is arrested at the time of their discharge from the sanatorium are much less likely to develop serious complications after their discharge.

That empyema is a serious complication of artificial pneumothorax cannot be questioned. Invariably the patient who develops empyema must be readmitted to the sanatorium for further treatment, and usually pneumothroax must be discontinued to be replaced by thoracoplasty or some other surgery. In only one case of the 14 in this series was pneumothorax not discontinued, and in this case no air has been given for over a year. The patient has been attending pneumothorax clinic for aspiration because, while the empyema cleared up under treatment, fluid persisted in considerable quantity. Five of the 14 cases died, a mortality of 36 per 100, over the ten-year period, four times the mortality of the pneumothorax cases that did not develop empyema.

Non-empyematous fluid, however, is in no sense a really serious complication of pneumothorax. Only 38 per cent of the individuals who had serous fluid needed to be readmitted to the Sanatorium for further treatment, while 47 per cent of those who at no time showed evidence of fluid were readmitted. Of the cases without fluid 11.8 per cent died, while the mortality among those who had serous fluid was only 6.2 per 100 during this ten-year period. While the differences between the percentages of readmissions or between the percentages of deaths are not significant, at least there is no evidence here that patients who develop fluid are any more likely to suffer relapse or to die soon after discharge from the Sanatorium than are those who do not at any time have fluid.

If we exclude those who developed empyema, the percentage discontinuing pneumothorax is the same for the group with fluid as for the group with no fluid, 22 per cent in each case. Pneumothorax was discontinued in 64 cases as far as our records show. In 11 of these 64 cases pneumothorax was discontinued after development of empyema, in 7 more because of the formation of uncomfortable amounts of clear fluid. One person discontinued his pneumothorax because of severe reactions from the treatment. Most of the others were unable to continue because of the formation of adhesions, but some gradually lost their collapse and a few just could not be bothered with keeping their clinic appointments. However, all except one patient continued their treatments for at least two years after pneumothorax was established in the Sanatorium. In this one case the left pneumothorax was replaced by thoracoplasty after five months because of the development of empyema. The right lung was still collapsed by fluid at the time of his readmission to the Sanatorium four years later.

This series provides no evidence as to just when pneumothorax may safely be

discontinued. Those who are now current at the pneumothorax clinic have been continuing their treatments from a few months to almost fifteen years. Of the 64 cases whose pneumothorax has been discontinued most of the patients continued their treatments for about four years, although the range was from five months to fourteen years. The average length of time that pneumothorax was continued for this group was 5.3 years.

For comparison with this group of 245 pneumothorax clinic patients we have the records of 680[2] discharged patients who attended the other clinics under the supervision of the Glen Lake Out-Patient Department. The two groups are quite comparable in most respects, but there is a much larger proportion of far advanced cases among the patients attending the pneumothorax clinic. Table 2 gives the percentage of cases having one or more readmissions to the Sanatorium from each of the two clinic groups, classified according to stage of disease at the time of their first discharge from the Sanatorium (for the pneumothorax clinic cases this is the first discharge after the establishment of pneumothorax).

There is a rather surprisingly large difference in percentage of cases readmitted to the Sanatorium from the pneumothroax clinic and from the other clinics.

TABLE 2

	PNEUMOTHORAX CLINIC		FAIRVIEW AND GLEN LAKE CLINICS	
	Number of cases	Number and per cent readmitted	Number of cases	Number and per cent readmitted
Far advanced	143	65 (45.5)	240	102 (42.5)
Moderately advanced	90	40 (44.4)	270	92 (34.1)
Minimal	12	6 (50.0)	143	15 (10.5)
Total	245	111 (45.3)	653	209 (32.0)

The difference is not significant for those whose tuberculosis was far advanced at the time of their first discharge from the Sanatorium, but it is very marked for those whose tuberculosis was in the minimal or moderately advanced stage. For the group as a whole the ratio of the difference between percentages of cases readmitted to its standard error is 3.71. The odds against a difference of such a magnitude being due to chance alone are approximately 5,000 to one. However, it is quite possible that this difference does not necessarily indicate that the progress of pneumothorax patients after discharge is less satisfactory than that of nonpneumothorax patients. Pneumothorax clinic patients are much more closely supervised than the other clinic patients and are much less likely to refuse to return to the Sanatorium when further treatment is advised by the clinic physician.

A comparison of the death rates over the ten-year period for the two groups indicates that the patients with pneumothorax have about the same prospect of survival after discharge from the Sanatorium as do the patients without pneumo-

[2] Twenty-seven cases with extrapulmonary tuberculosis only have been omitted from these comparisons of Fairview and Glen Lake Clinics with the Pneumothorax Clinic.

thorax. The percentage of deaths during the ten-year period from January, 1930 through December, 1939, from tuberculosis alone and from all causes, for the two groups is given in table 3.

There appears to be a fairly large difference between the two groups in percentage of deaths from tuberculosis, but this is due almost entirely to the larger proportion of far advanced cases among the pneumothorax patients. When the far advanced, moderately advanced and minimal cases are considered separately none of the differences between the pneumothorax and nonpneumothorax groups is significant. On the basis of the cases included in this study we cannot conclude that the pneumothorax patient has any better prospect of survival than does the nonpneumothorax patient. However, we hope to present at some uture date the results of a more detailed comparison of pneumothorax cases with discharged patients who have not had pneumothorax, based on the records

TABLE 3

	PNEUMOTHORAX CLINIC			FAIRVIEW AND GLEN LAKE CLINICS		
	Number of cases	Per cent Deaths from		Number of cases	Per cent Deaths from	
		Tuberculosis	All causes		Tuberculosis	All causes
Far advanced	143	13.2	13.2	240	8.3	12.1
Moderately advanced	90	4.4	6.7	270	6.7	10.4
Minimal	12	0.0	0.0	143	0.0	1.4
Total	245	9.3	10.2	653	5.8	9.0

TABLE 4

	NUMBER OF CASES	NUMBER AND PER CENT READMITTED	NUMBER AND PER CENT DEAD
Clinic	925	333 (36.0)	91 (9.8)
Nonclinic	2,776	550 (19.8)	574 (20.7)

of all patients discharged alive from the Sanatorium whether they have reported to our clinics or not.

We may compare the records of the 925 clinic patients with those of 2,776 discharged patients of Glen Lake Sanatorium who were alive at the beginning of the ten-year period under consideration and who did not report to any clinic after their discharge from the Sanatorium. Table 4 gives the percentage of cases with one or more readmissions to the Sanatorium, and the percentage that died during the ten-year period from January, 1930 to January, 1940 for all clinic cases and for discharged patients who did not attend clinic.

The two groups are perhaps not strictly comparable since only those clinic cases with definite diagnosis of tuberculosis were included in this study, while the nonclinic cases include a small proportion of cases not definitely diagnosed as tuberculous. However, the proportion of far advanced, moderately advanced

and minimal cases of pulmonary tuberculosis was about the same for the group who did not attend clinic as for those who did.

The mortality of the clinic patients during this ten-year period is a trifle less than half the mortality of discharged patients who did not attend clinic. Perhaps this lowered mortality among clinic patients may logically be explained as an effect of the closer supervision of the patients who attend clinic. Of course many of the patients report to their private physician for periodic examinations after their discharge from the Sanatorium, but there will always be those who neglect this precaution. And unless the physical symptoms of the reactivation of the tuberculous process are sufficiently marked, those who suffer relapse wait too long before taking steps to learn whether they need further treatment. Naturally their chances for recovery will not be as good as if the reactivation of the disease had been recognized earlier.

The percentage of cases having one or more readmissions to the Sanatorium is almost twice as great for clinic patients as for patients who did not attend clinic.

TABLE 5

	ARRESTED			NOT ARRESTED			TOTAL		
	Number of cases	Readmitted		Number of cases	Readmitted		Number of cases	Readmitted	
		Number	Per cent		Number	Per cent		Number	Per cen
Relief	141	46	32.6	120	66	55.0	261	112	42.9
Nonrelief	415	77	18.6	249	144	57.8	664	221	33.3
Difference			14.0			−2.8			9.6
$S.E._{difference}$			4.0			5.5			3.5
$\frac{Diff.}{S.E._{difference}}$			3.5			.51			2.74
Probability that this difference is due to chance alone			.0005			.61			.005

Ordinarily we think of readmissions as indicating relapse, since if the progress of the patient were satisfactory there would be no necessity for further sanatorium treatment. But in view of the fact that the mortality of this group of clinic patients is so much lower than that for nonclinic patients, it is rather difficult to believe that the progress of the patients who did not report to clinic was more satisfactory. It seems more likely that this larger group was not sufficiently closely supervised to find all of the cases needing additional sanatorium care. It is possible that a number of those who died during this ten-year period might have lived longer if the reactivation of their tuberculosis had been detected earlier.

It has been suggested that another reason for the greater percentage of relapses necessitating readmission to the Sanatorium from the clinic group may be that a fair proportion of them are living under conditions not exactly conducive to the maintenance of good health. Approximately 30 per cent of all clinic cases in this series were receiving direct relief, and it was felt that, in some cases

at least, the relief allowance was inadequate. In order to obtain some idea as to the effect of substandard living conditions on the health of tuberculous individuals, comparisons were made between those who were wholly or partially self-supporting and those existing on direct relief. The groups were divided according to condition on discharge from the Sanatorium because we know that patients whose tuberculosis is not arrested when they leave the Sanatorium are much more likely to have to return for further treatment. The results of the analysis are given in table 5.

The difference between the percentages readmitted from the relief and non-relief groups are significant for those classified as arrested on discharge from the Sanatorium and for the total of all cases. However, if we consider only those cases which were not arrested on discharge, we find practically no difference in the percentage of readmissions from the relief and nonrelief groups. Apparently it is true that the effect of sanatorium treatment is nullified to a considerable extent for those patients discharged in good physical condition when the conditions under which the patient must live after discharge are not conducive to the maintenance of good health.

SUMMARY

For this series of 245 pneumothorax cases treated at a clinic there was apparently no relationship between stage of disease or condition of the patient on discharge from the Sanatorium and the incidence of fluid which developed subsequently. However, the percentage of patients with fluid who developed empyema was almost five times as great for those whose tuberculosis was far advanced as for those whose tuberculosis was in the moderately advanced or minimal stage at the time of their discharge from the Sanatorium. It also appeared that it was much more likely that empyema would develop if the patient's tuberculosis was not arrested at the time of his discharge from the Sanatorium. The percentage of cases with fluid, as well as the percentage developing empyema, was in reasonable accord with the percentages reported in other studies of pneumothorax.

There was a much larger percentage of readmissions from the clinic group than from the group of discharged patients who did not attend clinic. However, the death rate for the clinic patients during the ten-year period was considerably lower than that for ex-patients who did not attend the clinic.

The percentage of readmissions from the group of clinic patients on direct relief was almost twice as great as that from the group that was wholly or partially self-supporting, for those cases that were discharged from the Sanatorium in good physical condition. Apparently the effect of Sanatorium care is nullified to a certain extent by substandard living conditions after discharge from the Sanatorium.

SUMARIO

En esta serie de 245 casos de neumotórax tratados en una clínica, no había al parecer relación alguna entre el período de la enfermedad o el estado del enfer-

mo al darlo de alta del sanatorio y la frecuencia del derrame que se presentó después. Sin embargo, el porcentaje de los enfermos en que había líquido y que manifestaron empiema, fué casi cinco veces mayor en aquéllos cuya tuberculosis estaba muy avanzada que en los que la tuberculosis se encontraba en un período moderadamente avanzado o mínimo al darlos de alta del sanatorio. También parece ser mucho más probable la aparición de empiema si no estaba estacionada la tuberculosis del enfermo al darlo de alta del sanatorio. El porcentaje de casos con líquido, así como el de los que manifestaron empiema, convino bastante bien con los porcentajes comunicados en otros estudios del neumotórax.

Fué mucho mayor el porcentaje de reingresos procedentes del grupo de la clínica que del grupo de antiguos pacientes que no asistieron a ésta. Sin embargo, la mortalidad entre los primeros fué mucho más baja durante el decenio que entre los segundos.

Entre los casos dados de alta del sanatorio en buen estado físico, el porcentaje de reingresos en el grupo de enfermos de la clínica que recibían socorros gubernamentales, fué casi dos veces mayor que en el grupo que se ganaba la vida por su cuenta del todo o en parte. Aparentemente, el efecto de la asistencia sanatorial queda anulado hasta cierto punto si las condiciones de la vida son subnormales después de salir del sanatorio.

BIBLIOGRAPHY

(1) Brock, B. L., Mullen, A. B., and Woodson, T. A.: Tuberculous effusions complicating artificial pneumothorax, Am. Rev. Tuberc., 1937, *35*, 548.

(2) De Cecio, T., and Potter, B. P.: The management of pleural effusions complicating artificial pneumothorax, Ibid., 1939, *40*, 272.

(3) Diamond, S., and Ivey, H. T.: Artificial pneumothorax in patients over forty, Ibid., 1941, *43*, 475.

(4) Eglee, E. P., and Jones, O. E.: A review of one hundred re-expanded cases of artificial pneumothorax, Ibid., 1937, *35*, 500.

(5) Jennings, F. L., and Mattill, P. M.: Accidents and complications in artificial pneumothorax, Ibid., 1940, *41*, 38.

(6) Jennings, F. L., Mattill, P. M., and Nemec, F.: Artificial pneumothorax, Ibid., 1940, *42*, 431.

(7) Kendall, W. B.: Artificial pneumothorax, Ibid., 1925, *12*, 209.

(8) Myers, J. A.: Artificial pneumothorax in the treatment of progressive minimal pulmonary tuberculosis, Ibid., 1935, *31*, 518.

(9) Myers, J. A.: Artificial pneumothorax: with special reference to the ambulatory patient, J. Thoracic Surg., 1937, *6*, 513.

(10) Potter, B. P.: Results of collapse therapy, Am. Rev. Tuberc., 1941, *43*, 184.

(11) Cutler, I. L.: Tuberculous empyema, Ibid., 1941, *43*, 197.

(12) Smart, E. P.: Empyema in pulmonary tuberculosis, J. Thoracic Surg., 1934, *3*, 413.

(13) Tice, F.: The ambulatory pneumothorax clinic and its place in a public health program, Dis. of Chest, 1939, *5*, 22.

(14) Tice, F., and Hruby, A. J.: Collapse therapy at Chicago Municipal Tuberculosis Sanitarium, A critical study of 8083 cases, J. A. M. A., 1939, *113*, 101.

(15) Weisman, J. I.: Effusions following artificial pneumothorax, Am. Rev. Tuberc., 1936, *33*, 522.

PANEL DISCUSSION

TREATMENT OF POSTOPERATIVE PULMONARY COMPLICATIONS

From the Point of View of the Surgeon[1, 2]

JOHN ALEXANDER

So-called postoperative pneumonia is not primarily a lobar or bronchial pneumonia but is primarily bronchial obstruction from retention of secretions, from which atelectasis and bronchial pneumonia are likely to develop and which may lead to pulmonary abscess or bronchiectasis. While the sulphonamide drugs are helpful in combating infection, they are useless in overcoming the fundamental cause of the illness, namely, retention of secretions.

Prevention and treatment of postoperative pneumonia must be directed toward keeping the tracheobronchial tree as free of secretions as possible before, during and after operation. Before operation, voluntary coughing, postural drainage, expectorants, the Trendelenburg position of the bed and bronchoscopy should be used according to the indications. During the operation, the following measures should be used: removal of pharyngeal secretions that might be aspirated into the lung, and of tracheobronchial secretions if an intratracheal tube is being used for anesthesia; a 10 or 15 degree Trendelenburg position of the operation table; hyperventilation of the lungs at frequent intervals; no preoperative narcotic or anaesthetic agent should be used that produces unconsciousness or semiconsciousness for more than a very short time after the completion of the operation.

Voluntary cough and expectoration at frequent intervals are the simplest and most useful measures after operation. Their effectiveness is increased (*1*) by encouragement of the patient to cough and manual support of the incision by the nurse or surgeon; (*2*) by the taking of several deep breaths before coughing; (*3*) by changes of posture from side to side and to the supine position, and from the Trendelenburg to a partially sitting position; (*4*) by occasional small doses of opiates to alleviate pain but not large enough to obtund the cough reflex; (*5*) by inhalations of 10 or 15 per cent carbon dioxide in oxygen if the patient is unwilling to breathe deeply before coughing; (*6*) by steam inhalations, hot mouth washes or drinks and expectorants. Collateral aids to effective cough and expectoration are oxygen inhalation for dyspnoea or a laboring heart, relief of abdominal distension and adequate support for an area of parodoxical movement of the thoracic wall that has been produced by a too extensive resection of ribs.

The measures listed in the last paragraph usually suffice to prevent postoperative pneumonia if they are used early, intelligently and faithfully, but in some

[1] Presented in the Panel Discussion before the Medical Section at the 38th annual meeting of the National Tuberculosis Association, Philadelphia, Pennsylvania, May 6, 1942.

[2] From the Department of Surgery, University of Michigan, Ann Arbor, Michigan.

cases the patient is unable to keep his tracheobronchial tree clear of secretions, perhaps only because treatment was begun too late. Then, the removal of the secretions by bronchoscopic aspiration or by Cameron Haight's tracheobronchial catheter suction is virtually the only way to save the patient from a grave or fatal pulmonary infection.

If effective preventive measures have not been employed, active treatment obviously should be used at the first signs of retention of bronchial secretions. These are: (*1*) a wet cough, persisting after expectoration; (*2*) persisting rhonchi, wheezes and râles, especially in one or both pulmonary bases, that are best heard during and after deep breathing or coughing; (*3*) progressive dyspnoea, cyanosis and fever; (*4*) roentgenological evidence of hypoventilation, atelectasis and bronchial pneumonia usually follow the other signs.

Other phases of postoperative pulmonary complications will be considered in the panel discussion. The reader is referred to an up-to-date article by Haight and Ransom on postoperative atelectasis and bronchial pneumonia in the August, 1941 issue of the Annals of Surgery.

POSTOPERATIVE PULMONARY COMPLICATIONS

From the Point of View of the Internist[1, 2]

H. McLEOD RIGGINS

The most important postoperative pulmonary complications are pulmonary infections, infarction and atelectasis. The most common pulmonary infection is lobular or bronchopneumonia; less common are suppurative pneumonia or lung abscess, bronchogenic spread in tuberculosis patients and, rarely, lobar pneumonia. Postoperative true atelectasis is only occasionally seen on our services at Bellevue and Triboro Hospitals. While it is not intended to minimize the importance of postoperative atelectasis, a résumé of the literature leads to the rather definite conclusion that its frequency has been over emphasized. King reported that atelectasis comprised 47 per cent of all postoperative pulmonary complications in a large series of surgical cases he studied on the General Surgical Services of the Massachusetts General Hospital during 1930 and 1931. However, in 39 per cent of his 200 cases of atelectasis, the diagnosis was made on physical examination alone. There is no mention of diagnostic or therapeutic bronchoscopy in any of his 200 cases. On the basis of the criteria which he used for the diagnosis of atelectasis, one is reluctant to accept this high incidence of postoperative atelectasis. Coryllos advanced the theory that all pneumonias begin as atelectasis. This theory has been refuted by numerous observers. In our experience, atelectasis has not infrequently been confused with hypoventilation, lobular pneumonia and occasionally pulmonary infarction. The writer has mistakenly advised bronchoscopy in several instances where atelectasis was erroneously diagnosed. A more critical analysis of the physical findings, chest roentgenograms and clinical picture should have led to the correct diagnosis of aspiration pneumonia. Bronchoscopy revealed no cause for atelectasis and subsequent events proved the condition to be bronchopneumonia.

The fact that postoperative pulmonary infections, especially lobular pneumonia combined with hypoventilation of the lungs, are at times mistaken for atelectasis is understandable when it is realized how often the clinical diagnosis of atelectasis is influenced by the roentgenological findings and opinion. Portable chest roentgenograms are frequently used and greatly relied upon in the postoperative examination of the lungs. Their easy accessability and frequent use may result in too occasional and perhaps casual physical examination of the chest postoperatively. Postoperative physical findings, too, are often significantly altered by the effects of the operative procedure, particularly if thoracic or upper abdominal surgery has been done. Also, as a rule, the preoperative and postoperative observers are not the same. These and other factors combined

[1] Presented in the Panel Discussion before the Medical Section at the 38th annual meeting of the National Tuberculosis Association, Philadelphia, Pennsylvania, May 6, 1942.

[2] From the Department of Practice of Medicine, College of Physicians and Surgeons, Columbia University and Bellevue Hospital, New York.

with the inherent difficulties in the differential diagnosis of atelectasis, pulmonary infections, pleural effusion, serum in the soft tissues of the chest wall following thoracic surgery, often lead to considerable confusion on the part of the physician and perhaps occasionally his too ready acceptance of the roentgenological diagnosis of "atelectasis."

Postoperative atelectasis is likely to occur in patients with tuberculosis and bronchial stenosis following upper-stage thoracoplasty. The resulting relaxation of the affected part of the lung, the distortion and kinking of the already stenosed and partly occluded bronchus may lead to complete bronchial occlusion with at least partial atelectasis of the related lobe. However, even in such cases, the atelectasis in all probability is only partial. Complete occulsion of a lobar bronchus of a lobe containing extensive tuberculosis with cavitation is almost certain to result in retention of infectious secretions, with superimposed mixed pyogenic infection and patchy atelectasis. In such cases, bronchoscopic aspiration of infectious secretions may be a life-saving procedure. It may be necessary for the bronchoscopist to pass the suction tube beyond the area of occlusion in order to aspirate effectively secretions distal to the occlusion. The preoperative treatment of such diseased bronchi with the destruction or removal of granulation tissue, if possible, to facilitate more adequate bronchial function is an important pre-thoracoplasty consideration. Parenthetically, our observations on serial intracavitary pressures in cases with bronchial stenosis or partial occlusion and positive pressure cavities lead us to believe that often bed-rest alone may result in considerable improvement of the bronchial function as evidenced by decreased positive intracavitary pressure. It has been noted that, in patients whose pulmonary disease tends to improve on bed-rest, the bronchial disease also is likely to improve somewhat. Pre-operative bed-rest, bronchoscopic observation and treatment, if necessary, of patients with bronchial disease with stenosis or partial occlusion may prevent such serious post-thoracoplasty complications as bronchopneumonia, mixed pyogenic and tuberculous infection and patchy atelectasis. Such complications are usually diagnosed as atelectasis. More often, they are atelectasis and infection.

The development of postoperative pneumonia is influenced by several factors, not the least important of which are acute, subacute or chronic upper respiratory infections, or bronchitis, prior to or at the time of the operation. It has been pointed out by many that males are much more likely to develop postoperative pneumonia than are females. This is in line with the fact that the incidence of pneumonia is greater in males than it is in females irrespective of surgery.

The postoperative pneumonias are rarely lobar in type but are usually lobular and occasionally suppurative. The bacteriology of the sputum or bronchial secretions is usually of no specific type. As a rule, streptococci, pneumococci, staphylococci and not infrequently gram-negative bacilli are present in a single specimen. The pneumococci are usually of the higher types. Toxaemia, anoxaemia, dyspnoea and cyanosis vary greatly depending upon the severity, extent and type of the pulmonary infection, the degree of ventilatory insufficiency and cardio-circulatory disturbance. Severe anoxaemia may lead to cardio-

circulatory failure, perhaps shock and death. Mild pulmonary infections, particularly in patients with rather good respiratory and cardio-circulatory reserve may result in very few symptoms.

The physical findings over the chest also vary greatly, depending upon a number of factors. If upper abdominal surgery has been done, there may be considerable splinting of the diaphragm, shallow breathing with resulting hypoventilation. In such cases, the percussion note may be impaired and the breath sounds diminished especially near the lung bases. Also, because of pain, the patient may not be able to take a deep breath just before a roentgenogram is taken and, as a rule, the examination is done in the recumbent or semirecumbent position. All of these factors contribute to rather poor aeration, especially of the bases of the lungs with more or less obscuration of the costophrenic sulci and perhaps of the diaphragm. These findings are likely to suggest "atelectasis" to the roentgenologist. If the patient also has patchy lobular pneumonia, the roentgenological findings are even more likely to suggest atelectasis. In many of these cases, the physical examination is of greater value than portable roentgenograms, particularly if one fails to take into consideration the various factors enumerated above which lead to hypoventilation, elevation of the diaphragm, etc.

If the patient is placed in the lateral position, as suggested by Haight and Ransom, and the uppermost lung examined, particularly during deep breathing and after coughing and following measures to reduce pain, the breath sounds are likely to become more audible where previously they may have been distant or absent, and rhonchi are likely to be elicited if bronchial secretions are present.

If atelectasis of a lobe or of an entire lung is present, usually there is marked dyspnoea or orthopnoea, evidence of severe anoxaemia, cyanosis and perhaps marked cardio-circulatory disturbance as a result of the pulmonary insufficiency and the anoxia. These symptoms and findings are usually more pronounced in the presence of extensive atelectasis than they are in patients with bronchial or suppurative pneumonia. If extensive lobar atelectasis is present, there is usually marked dullness, diminished to absent breath sounds but *no* râles. In cases with bronchopneumonia, the note may not be greatly altered and, while the breath sounds may be diminished, they are rarely absent and post-tussive râles can usually be elicited. The presence of pulmonary râles is good evidence against the condition being lobar atelectasis.

The roentgen findings are usually of great help but may also be confusing. If the pulmonary complication is bronchopneumonia or spread of the tuberculosis, usually mottling, which may or may not be fairly confluent, is present. If there is atelectasis of a lobe or of the entire lung, the characteristic roentgen finding is homogeneous clouding. However, homogeneous clouding is usually present over the site of the thoracoplasty operation and may occasionally extend to the diaphragm even though only portions of three or four ribs have been removed. This clouding is usually due to a number of factors, the more important of which are serum in the soft tissues of the chest wall and collapse (not atelectasis) of the lung from thoracoplasty. It may be of some importance to recall that the surgeon may carry the incision quite a distance below the most

distal rib removed. Serum may collect in the dependent part of the wound and cause extensive homogeneous clouding beyond the area of rib resection. Occasionally, pleural effusion may develop following thoracoplasty resulting in clouding throughout the operative side. Roentgen findings in many such cases may suggest atelectasis. Usually, however, after careful study of the physical findings, roentgenograms and the clinical picture, a correct diagnosis can be made.

Bronchogenic extension of the tuberculosis following thoracoplasty is often related in part to the amount and bacillary content of the sputum, the ability of the patient to rid the air passages of secretions and his lack of resistance to the disease. This last factor is often not accorded proper significance in the evaluation of postoperative bronchogenic spread of the tuberculosis. The careful selection of patients for thoracoplasty plays an important rôle in reducing the incidence of postoperative pulmonary complications. Probably the most important factor in preventing postoperative spread of the tuberculosis is the resection of portions of only two or three ribs at each staged thoracoplasty, as advocated by Alexander and his coworkers.

Tuberculosis may develop in the contralateral lung as a result of the aspiration of tuberculous fluid or pus from the pneumothorax space in patients with bronchopleural fistula. Not infrequently, extension of the tuberculosis into the "good" lung has been noted following thoracoplasty for obliteration of the empyema space, in patients having no demonstrable cavity or active disease in the "good" lung preoperatively.

These observations have led us to believe that all patients with tuberculous empyema and candidates for thoracoplasty should be studied carefully to determine if a previously undetected bronchopleural fistula is present. Careful manometric readings of the intrapleural pressures immediately after thoracocentesis may demonstrate a patent bronchopleural fistula. If negative intrapleural pressures gradually become positive within a few minutes after thoracocentesis, a valve-like fistula is probably present. Gas should be removed from the pleural space for analysis. If the O_2 content of the gas is above 0.35 per cent and the CO_2 content is below 10 per cent, the chances of a bronchopleural fistula being present are good. Often, following the injection of 5 or 10 cc. of a 1 per cent aqueous solution of gentian violet into the empyema space and proper positioning of the patient, a patent fistula can be diagnosed if the patient raises sputum containing the dye, which may occur within a few minutes or a few hours. In some cases where the fistula is intermittently patent, the dye may not be raised for several days. Most bronchopleural fistulae develop near the visceral attachment of pleural adhesions or in the immediate vicinity where cavities are, or have been present. It is of practical importance to make sure that this area of the lung is brought in contact with the dye-stained fluid. Bronchopleural fistulae are frequently patent only intermittently. For this reason, all studies at a given time may be entirely negative. It should also be emphasized that quite often patients may have a patent pleural fistula without having pyogenic pleural infection. Pyogenic pleural infection in pneumothorax patients is reason to suspect strongly the presence of a broncho-

pleural fistula. This is especially true if pneumococci, streptococci or mixed pyogenic organisms are present. However, absence of pyogenic organisms in tuberculous empyemas does not rule out bronchopleural fistula.

In view of the possibility of bronchopleural fistula being present in all cases of tuberculous empyema complicating pneumothorax, the question frequently arises whether or not tube drainage should be done prior to thoracoplasty for obliteration of the empyema space. Our experience has led us to believe that tube drainage is not indicated in all cases of tuberculous empyema with or without demonstrable pleural fistula. If the fistula is persistently present and obviously of fairly large size, as evidenced by copious expectoration of dye-stained sputum or pus, tube drainage prior to thoracoplasty should be done, even though pyogenic pleural infection is not demonstrable. The danger of aspiration of the empyema contents into the contralateral lung is obvious. However, if the pleural fistula is intermittently patent and obviously very small, as indicated by rare expectoration of only slightly dye-stained sputum, and by other tests, such patients may undergo thoracoplasty without tube drainage and usually without spread of the disease to the "good" lung. However, in these patients the empyema contents should be aspirated immediately before operation and the pleural space drained dry. Local anesthesia for the thoracoplasty may be preferable and safer. The position of the patient during and immediately after operation is important. The prompt removal of bronchial secretions during and immediately after operation is also of great importance.

Occasionally, temporary phrenic paralysis, in cases with the lung attached to the upper thorax and to a movable diaphragm, may relax the lung and reduce the size of the fistula sufficiently so that thoracoplasty may be done without too great a risk of spread to the "good" lung as a result of aspiration of infectious secretions through the fistula during operation. Patients having mixed pyogenic and tuberculous empyema and a bronchopleural fistula, and who are candidates for thoracoplasty, should have preoperative tube drainage.

Pulmonary infarction is a comparatively rare complication in thoracic surgery. It is more likely to follow abdominal or pelvic surgery, or the ligation of the saphenous vein, if this is not done at the junction of the saphenous and femoral veins. Thrombi of the veins may become dislodged several days postoperatively, frequently after the patient is up and about. Once dislodged, the emboli are returned to the right heart and thence to one of the pulmonary arteries, a branch of which may become occluded and pulmonary infarction results.

The symptoms and physical findings of infarction depend largely upon the extent of the infarction and subsequent developments. If the infarction is extensive, pleural pain may be most severe and the patient may go into shock. Blood-streaked or bloody sputum may or may not be present. Usually, there is considerable cough, frequently unproductive. Dyspnoea, orthopnoea, anoxaemia and cardio-circulatory changes vary significantly, depending upon the extent of the infarction and depletion of the respiratory and cardio-circulatory reserve. Symptoms may vary from severe shock to slight pleural pain and unproductive cough. If the area of infarction undergoes absorption, there may be no expec-

toration. However, if necrosis and liquefaction occur, cough and expectoration develop and cavity may become demonstrable on the roentgenogram.

Abnormal physical findings may be scanty or entirely absent. Areas of dullness and diminished breath sounds, a pleural friction rub or pleural râles may be noted. If necrosis and liquefaction develop, medium and coarse râles are usually demonstrable. Occasionally, secondary pleural effusion develops. Thoracocentesis may reveal thin, usually sterile, occasionally blood-tinged fluid.

PREVENTION OF POSTOPERATIVE PULMONARY INFECTIONS

In view of the fact that postoperative pulmonary infections may be significantly related to upper respiratory infection prior to, or at the time of, operation, the presence of such infection should be diligently sought for preoperatively. Haight and Ransom emphasize that, if surgery is of an elective nature, it should not be performed, as a rule, until some weeks after the upper respiratory infection has completely cleared. In patients having considerable amounts of purulent sputum, especially in those having lung abscess or bronchiectasis, every effort should be made to rid the respiratory system of all secretions prior to and during operation. Postural drainage should always be done just prior to operation and preoperative bronchoscopy may be needed occasionally to aspirate secretions in this group of patients. If the more simple measures, including cough and expectoration and postural drainage have been effective, bronchoscopy is usually not necessary. Patients having large quantities of sputum frequently expectorate most of it during the forenoon. For this reason it is desirable to postpone surgery in these patients when practicable until the afternoon. During the past year, most of our patients at Triboro Hospital having large amounts of sputum with a high Gaffky count, have been operated upon in the afternoon. Our surgical staff shares the belief that the incidence of postoperative pneumonia and bronchogenic spread of tuberculosis has probably been reduced by operating on these patients in the afternoon.

Proper oral hygiene is also important preoperative treatment. In this connection, we have rarely seen suppurative pneumonia or lung abscess develop in edentulous patients, whereas most of our patients with lung abscesses, have poor oral hygiene. These observations suggest the great importance of improving the oral hygiene preoperatively.

The selection of preoperative and postoperative sedation should be done with great care. Drugs which prolong unconsciousness unduly, or inhibit the cough reflex, should not be given. We thoroughly agree with Alexander, Haight and Ransom that it is most important for the patient to regain consciousness, to take deep breaths and cough as soon after the operation as possible.

Paradoxical breathing and paradoxical cough are frequently present after thoracoplasty, especially if long portions of too many ribs have been removed. They are more likely to develop after second- or third-stage thoracoplasty and especially if long anterior portions of ribs have been resected. Paradoxical respiration and cough greatly increase the difficulty of raising secretions, the retention of which is likely to lead to postoperative bronchopneumonia or spread

of tuberculosis. The removal of shorter portions of fewer ribs at each staged thoracoplasty, as advocated by Alexander and his group, has undoubtedly been one of the greatest contributions in recent years in the prevention of postoperative spread of tuberculosis.

It should be emphasized that the tuberculosis patient may also develop nontuberculous bronchopneumonia following thoracoplasty or general surgery. Postoperative nontuberculous pulmonary infections in tuberculosis patients are likely to be regarded as tuberculous in nature. If there is a possibility that such infections may be of a mixed or nontuberculous nature, the prompt administration of one of the sulfonamides, preferably sulfadiazine, is advisable. Nontuberculous postoperative pneumonia, especially suppurative pneumonia, not infrequently plays an important rôle in the exacerbation of previously quiescent tuberculous foci. If the pneumonia is of a suppurative nature due to anaerobic infection, usually none of the sulfonamides is of benefit.

Frequent changing of the patient's position postoperatively, the use of the Trendelenburg position, periodic encouragement of the patient to take deep breathing exercises followed by effective coughing, the use of shot bags or other measures to counteract paradoxical respiration and cough, sufficient medication to relieve severe pain without interfering with the cough reflex, the use of hot drinks and occasionally steam inhalation are practical measures of great importance in the prevention of postoperative pulmonary infections. Because of their simplicity and routine nature, they may often be overlooked. Special nurses trained in the importance of these routine measures are an essential part of any team in the successful postoperative care of these patients. Eternal vigilance and attention to minute detail is the price of prevention and salvation of many patients from postoperative pulmonary complications.

TREATMENT OF POSTOPERATIVE PULMONARY COMPLICATIONS

The most effective and best treatment of postoperative pulmonary complications is prophylaxis. It has been emphasized that the development and retention of infectious bronchial secretions are dangerous and often lead to pulmonary infection and occasionally to atelectasis. Every effort should be made to keep the upper air passages and stem bronchi free of secretions during and immediately after operation. If the simple measures which have been discussed for doing this are not entirely successful, the introduction of a bronchial catheter, as suggested by Haight and Ransom, should be resorted to promptly. Should this method not meet with success, bronchoscopy may be necessary occasionally. When it is necessary, it should be done promptly. Retention of excessive infectious secretions over night or even for a few hours may lead to the development of pneumonia, bronchogenic spread of tuberculosis and occasionally to atelectasis. Should lobular or lobar pneumonia threaten, or develop, one of the sulfonamides, preferably sulfadiazin, should be given immediately.

SUMMARY

1. Despite great advances in general and thoracic surgery and anaesthesia, postoperative pulmonary complications remain a frequent and serious hazard.

2. The majority of these complications have their genesis in the development and retention of infectious bronchial and pulmonary secretions.

3. The prevention, insofar as possible, and the prompt removal of bronchial secretions, both during and after operation by the various methods discussed, should greatly reduce the incidence of serious postoperative pulmonary complications.

4. Postoperative pulmonary complications are usually inflammatory in nature; simple atelectasis and infarction are comparatively rare.

5. Males are much more likely to develop postoperative pulmonary complications than are females.

6. If lobular or lobar pneumonia threatens (extensive secretions present) or develops, sulfadiazin should be given immediately.

7. Eternal vigilance, attention to minute detail by anaesthetist, surgeon, nurse and internist, is the price of prevention and salvation of many patients from postoperative pulmonary complications.

SUMARIO

1. A pesar de los grandes adelantos obtenidos en la cirugía general y torácica y la anestesia, las complicaciones pulmonares postoperatorias continúan representando un peligro frecuente y grave.

2. La mayoría de esas complicaciones tienen su origen en la producción y retención de secreciones bronquiales y pulmonares infecciosas.

3. La profilaxia, en todo lo posible, y la rápida eliminación de las secreciones bronquiales, tanto durante la operación como después, con las varias técnicas expuestas, deben rebajar considerablemente la frecuencia de las complicaciones pulmonares postoperatorias graves.

4. Las complicaciones pulmonares postoperatorias, suelen ser de naturaleza inflamatoria, siendo comparativamente raras la atelectasia simple y el infarto.

5. Los varones son mucho más susceptibles que las mujeres de mostrar complicaciones pulmonares postoperatorias.

6. Si amaga o aparece una neumonía lobulillar o lobular (con mucha secreción) hay que administrar inmediatamente sulfadiazina.

7. La vigilancia constante, la atención a los pormenores más ínfimos por el anestesiador, el cirujano, la enfermera y el interno, constituyen el precio que hay que pagar por la profilaxia y salvación de muchos enfermos en las complicaciones pulmonares postoperatorias.

REFERENCES

(1) Alexander, J.: Preoperative and postoperate care of patients with surgical diseases of the chest, Arch. Surg., 1940, *40*, 1133.

(2) Alexander, J.: The Collapse Therapy of Pulmonary Tuberculosis, Charles C. Thomas, 1937.

(3) Coryllos, P. N.: Postoperative pulmonary complications and bronchial obstruction; postoperative bronchitis, atelectasis (apneumotosis and pneumonitis), considered as phase of the same syndrome, Surg., Gynec. & Obst., 1930, *50*, 795.

(4) Haight, Cameron, and Ransom, Henry K.: Observations on the prevention and treatment of postoperative atelectasis and bronchopneumonia, Ann. Surg., 1941, *114*, 243.

(5) King, D. S.: Postoperative pulmonary complications. (1) A statistical study based on two years' personal observation, Surg., Gynec. & Obst., 1933, *56*, 43.

TREATMENT OF POSTOPERATIVE PULMONARY COMPLICATIONS

From the Point of View of the Pathologist[1, 2]

MAX PINNER

Many postoperative complications following thoracic surgery can be avoided if patients are preoperatively submitted to proper respiratory function tests. No surgeon would think of removing one kidney without having ascertained that the remaining kidney is functionally competent, but still many thoracoplasties, lobectomies and pneumonectomies are performed without even an attempt to determine the respiratory capacity of the patient or of the contralateral lung. The usual estimation of the vital capacity is just about as informative as would be the measurement of the bladder capacity in renal surgery. In many cases it is misleading, since reasonably good vital capacities are found in patients with extremely poor respiratory reserve.

Adequate functional test should at least include standard spirometric studies under basal conditions and following exercise and the determination of the maximum breathing capacity. Depending on the outcome of these studies, blood-gas analyses may be indicated and in many cases the function of each lung separately by bronchospirometry should be measured. The latter procedure is particularly advisable before undertaking extensive and irreversible collapse operations and pneumonectomies. It must be stressed that clinical and roentgenological criteria are frequently misleading guides for the estimation of the functional capacity of one lung. After having made nearly 300 bronchospirometric examinations, we are impressed by the fact that sequelae of pathological processes, that are clinically and roentgenologically often much less obvious than parenchymal lesions, cause not infrequently unexpectedly severe impairment of function. Following dry and wet pleurisies, and particularly empyemata and absorption of pneumothoraces, lungs frequently have a severely decreased ability to absorb oxygen, although few roentgenological changes are evident and although their vital capacity may be not much reduced. Bronchospirometry is the only reliable method of measuring the function of such lungs. We believe that if the processes just mentioned have occurred on the contralateral side, bronchospirometry is urgently indicated in order to avoid the disaster of respiratory failure following operation.

The discomfort caused for the patient by bronchospirometry is in average less than that caused by bronchoscopy. We have not encountered any serious ill effects. Two patients developed nonspecific bronchopneumonia which resorbed completely. It seems, therefore, justifiable to recommend strongly the routine use of bronchospirometry, at least in all cases in which any reasonable doubt exists as to the functional competence of the contralateral lung. And be it repeated, such doubt must often be based not only on actual findings but on past history.

[1] Presented in the Panel Discussion before the Medical Section at the 38th annual meeting of the National Tuberculosis Association, Philadelphia, Pennsylvania, May 6, 1942.

[2] From the Montefiore Hospital for Chronic Diseases, New York.

TREATMENT OF POSTOPERATIVE PULMONARY COMPLICATIONS

From the Point of View of the Bronchoscopist[1, 2]

LOUIS H. CLERF

From the standpoint of the bronchoscopist, important postoperative complications are aspiration of foreign body, postoperative pulmonary atelectasis and pulmonary abscess.

The best treatment for foreign body is prevention. This entails removal of dentures and careful checking of teeth before and after operation, also checking of portions of tissue removed and checking of sponges, instruments, etc. in nasal or oral operations. If a foreign body is aspirated into the air passages the only treatment is bronchoscopic removal.

Postoperative atelectasis resulting from accumulation of secretions in a bronchus may be treated successfully by bronchoscopic aspiration if the more conservative methods of treatment have not given relief. While prevention should be practiced, this is a bronchoscopic problem only when there is a large quantity of secretion in the tracheobronchial tree during, or at the termination of, the operative procedure. If there is present at the completion of an operation an excessive quantity of secretion, it may be removed by bronchoscopic aspiration or with the aid of a catheter.

If atelectasis does occur and relief cannot be secured by the commonly employed simple measures, bronchoscopic removal of the secretions can be accomplished and should be resorted to promptly. This can be done without serious distress to the patient and without removing him from his bed.

Since the nonsurgical treatment of pulmonary abscess is dependent upon the establishment and maintenance of adequate drainage, bronchoscopy should play a very important part, particularly in a recent abscess. If drainage is impaired by granulation tissue, inspissated secretion or other forms of obstruction, much can be accomplished by prompt bronchoscopic aspiration. It is necessary to localize accurately the bronchial subdivision which drains the pus from the abscess and to utilize appropriate aspirators. Often, shrinking of inflammatory mucosa and removal of granulation tissue about the orifice of the discharging bronchus will materially aid in getting rid of the contents of the abscess. It is important, when considering bronchoscopic treatment, that this be carried out only for a relatively short time and if there is no prompt response then surgical measures should be resorted to.

[1] Presented in the Panel Discussion before the Medical Section at the 38th annual meeting of the National Tuberculosis Association, Philadelphia, Pennsylvania, May 6, 1942.

[2] From the Jefferson and Pennsylvania Hospitals, Philadelphia.

TREATMENT OF POSTOPERATIVE PULMONARY COMPLICATIONS

From the Point of View of the Nurse[1, 2]

ALICE LOVE MANNING

During the past few years thoracic surgery has offered another specialty in nursing. Regardless of how much nursing in general surgery a nurse has done, the care of thoracic patients is far different. It is not only during the immediate postoperative period but for weeks and months following the operation that the patients must have special attention. The patient's immediate welfare and the prevention of complications following the operations depend in great part upon the nurse's ability, intelligence and judgment.

My personal interest in the management of postoperative complications consists of three different phases. The first is teaching nurses the important points in the postoperative care of patients undergoing thoracic surgery.

The second is making certain that, when the patient returns from the operation room, a nurse stays with the patient and makes certain that he receives the proper care, as prescribed by the surgeon. The supervision during the postoperative period has as a primary interest the patient and his needs. Other than the patient's welfare, the economy of nursing energy and hospital equipment must be considered.

The third responsibility is the frequent checking of the status of the patient's shoulder exercises, X-ray and laboratory work postoperatively, and the orders for the preparation for any following operative stages.

[1] Presented in the Panel Discussion before the Medical Section at the 38th annual meeting of the National Tuberculosis Association, Philadelphia, Pennsylvania, May 6, 1942.

[2] From the State Hospital for Incipient Tuberculosis, Ray Brook, New York.

TUBERCULOSIS IN ENGLAND DURING WAR[1, 2]

J. B. McDOUGALL[3]

The summer of 1939 found the Tuberculosis Service in England at as high a pitch of perfection as it had ever attained since the inauguration of a national tuberculosis scheme in 1911. Twenty-eight years of hard work had produced something more than a reduction in the mortality rate in the disease. Sanatoria were well equipped; waiting lists were, with very few exceptions, down to a minimum; modern methods in treatment, including major thoracic surgery, were fast becoming the order of the day in selected Sanatoria; and few of the large centres for diagnosis and treatment were without modern X-ray apparatus. On the administrative side valuable work had been done, especially since the last war, in the publication of reports on nearly every aspect of tuberculosis work and the Joint Tuberculosis Council of England, with its thirty odd representatives from the various societies interested in tuberculosis in this country, had issued the most valuable contributions on such varied subjects as *Tuberculosis amongst Nurses, Results of Artificial Pneumothorax Treatment, The Examination of Contacts, Skiagraphic Terminology* and *Rehabilitation.* Nevertheless in this same summer of 1939 there was a feeling that the new buildings which the Ministry of Health were erecting on the sites of sanatoria and other hospitals in different parts of the country were for grimmer purposes. Innumerable visits were paid by Government officials to selected centres in connection with preparations for possible war. All this was the forerunner of an emergency which few had imagined possible a few years previously. The month of August, 1939, brought most of us who had been enjoying our annual holiday rushing back to prepare for the very events which came to pass on September 3, 1939.

Within the brief spell of twenty-four hours many sanatoria in this country were transformed from a peace-time to a war-time basis. The new buildings which had been erected in the quiet of the summer, which was fast going, were staffed with nurses and doctors ready to deal with medical and surgical emergencies of an entirely different kind from those associated with the tubercle bacillus. Less than an hour after our Prime Minister had spoken we had our first air raid warning and we waited for some hours to receive the casualties which had been threatened. Although outwardly there was no sign of panic there was nevertheless a genuine desire on the part of large numbers of patients in sanatoria all over the country to return to their homes and to ensure the safety of their near relatives. At other institutions many patients with tuberculosis were discharged to make room for air-raid casualties which were thought to be inevitable.

[1] Submitted on behalf of the Council of the National Association for the Prevention of Tuberculosis, London, England.

[2] Presented by Dr. G. J. Wherrett (Ottawa, Canada) before the Joint Session of the Medical and Administrative Sections at the 38th annual meeting of the National Tuberculosis Association, Philadelphia, Pennsylvania, May 9, 1942.

[3] Medical Director, Preston Hall Sanatorium, Maidstone, Kent.

In the towns, evacuation took place on a large scale and, before one week of war had passed, disorganization of our peace-time footing had made itself felt. Tuberculosisd ispensaries were unable to devote all their energies to their immediate task because tuberculosis officers were called upon to undertake air-raid precautions work. Many medical superintendents of sanatoria were forced to disinfect rooms, beds and bedding and to administer in addition a large general hospital established in the near neighbourhood of the sanatoria which had only a week before been their sole responsibility. It is easy to be wise after the event. Experience has shown that the ultra-elaborate precautions were unnecessary; that many patients who left sanatoria need not have done so; that the bombing which we had anticipated failed to become a fact and it was only towards the end of 1939 that some effort was made to return to the normal tuberculosis service.

Many of us were well aware that an organization which was difficult to keep moving perfectly in time of peace had been seriously interrupted by nothing more than a few weeks of war. We knew that hundreds of our cases of open tuberculosis were being uncared for according to our peace-time standards and that it only required time to bring to our notice the evil harvest of this effect. An early review published by Stocks (Lancet, 1040, *1*, 725) showed that in London there was in 1940 a pronounced increase during the winter months of pulmonary tuberculosis, bronchitis and other respiratory affections amongst young adults. The first step in reorganization was to put into commission afresh many of the beds which had been compulsorily taken over by the Ministry of Health for air raid precautions work and representations to the Minister of Health made possible the release of nearly 6,000 more beds for this purpose. As time went on and as the tempo of war became better understood, there was during 1940 a gradual but quite incomplete return to normal tuberculosis dispensary work. One of the greatest difficulties was presented by the evacuated tuberculous persons, for the areas into which they had gone were to a large extent rural areas and quite incompetent to deal with the influx and supervision of such numbers. The relative quiet of the summer of 1940 found many of the evacuated persons returning to their homes and constant representations were being made to the Minister of Health for the reëstablishment of the normal tuberculosis service.

Just when there was every evidence that normality was about to be attained, the bombing of large cities, including London, sufficed to disorganize all arrangements once again. No sooner had the evacuation from Dunkirk been successfully accomplished than beds in Emergency Medical Service hospitals began to fill with casualties and the fear which was potential in September, 1939, became stark reality in September, 1940. Thousands of the population in towns spent night after night in shelters; the forced billeting of cases of tuberculosis on healthy households was quite common; transport was to a great extent disorganized and for a time it was difficult to administer sanatoria, especially those which had Emergency Medical Service responsibilities to surmount in addition to routine work. With the destruction of many homes in London and other large centres

of population and with the resulting crowding of people under unhealthy hygienic conditions, and with wholesale evacuation of people to country districts, it was to be expected that an increase in tuberculosis would be inevitable. The winter of 1940–1941 was a severe experience for those of us who had sanatorium responsibilities in that area which the map shows to have been the field over which the Battle of Britain was won. It was a new and sometimes terrifying experience to be forced to crowd as many as 200 tuberculous patients in cellars and dungeons in the cold, dark hours of the long winter nights, when medical staff had frequently to run from dug-outs to attend to air raid casualties which arrived in numbers proportionate to the proximity of falling bombs. If September 15, 1940, is selected as a red-letter day in the history of Preston Hall, near Maidstone, it is only because it coincided with a night in which we had representatives of the nationalities of most of the Western European countries in our wards as patients, a not inconsiderable number being German airmen, French, Dutch, Belgian and others were relics from the evacuation from the Continent in the summer. In spite of all these administrative and clinical difficulties, however, many patients remained in sanatoria and whatever criticism may be levelled against the wholesale evacuation of patients from sanatoria in 1939, full credit must be given to the organization which made it possible for so many patients to remain in sanatoria in September, 1940. The Ministry of Health set up a Standing Advisory Committee on Tuberculosis to advise on ways and means of overcoming certain difficulties and the National Association for the Prevention of Tuberculosis together with the Joint Tuberculosis Council met as frequently as time and conditions permitted. Special attention was given to the problem of nutrition and rationing and the Standing Advisory Committee maintained a close touch with the Ministry of Food concerning the question of rationing and tuberculosis. It was possible, however, to devise a diet that was qualitatively and quantitatively adequate, although the diet was lacking much in the variety which was supplied in peace-time. The pronouncement of experts showed that it was possible to build up a well balanced diet containing necessary vitamins with rationing as it was. Our anxiety was not so much with the sanatorium patient as with the tuberculous patient living at home. Shortage of milk, eggs, butter and margarine was likely to prove a severe trial to the tuberculous patient, but cheese was substituted for eggs and margarine was given in sufficient quantities and, although the milk ration was reduced, it was still possible for a large number of local authorites to continue to administer extra nourishment for cases of active disease. Dealing with the food situation as a whole as applied to tuberculosis institutions, our experience has been that in times of severe bombing the difficulties are enormous, largely due to the inability to have food dispatched by transport. At other times (that is, in the relative lull from aerial attacks) the originality and initiative of kitchen staffs can overcome many problems which would have been considered insuperable in peace-time. Institutions which have ample space are now growing vegetables in places previously reserved as flower beds and the breeding of livestock, especially rabbits, is becoming a common practice in many districts, a policy encouraged by the

Ministry of Agriculture. Many of us, however, still feel that special consideration should be given to the tuberculous patient and the various voluntary organizations in this country are bringing every possible pressure to bear on the Ministry of Food to increase the amount of milk, especially to the dietary of the tuberculous. We realize that even the tuberculous cannot be supplied with peace-time rations but we are aiming hard at the happy medium and there is growing evidence that institutions especially are taking a growing and keener interest in the production of their own food supplies than they have ever done. The lack of cereals for the feeding of livestock makes the position even more difficult and in my own institution I have set up what amounts to a special department in which every piece of scrap which has not been consumed by patients and staff is collected and specially treated by heat and fed to livestock, with a view to making us more and more independent of outisde supplies as time goes on.

It is not only, however, in matters concerning general administration and food supplies that efforts have been made to maintain something approaching pre-war standards. In the province of rehabilitation great strides have in fact been made, for it has been found that institutions in England like Papworth and Preston Hall, which had a long and successful record in rehabilitation prior to the war, have switched over all their machinery and man power for government contracts with amazing and complete success. There is in fact a feeling that many institutions in this country could be doing more in this matter at present than they are doing, for never were orders more easy to obtain than during war time. In the year prior to the war Preston Hall, for example, sold to the public each year about $400,000 worth of goods; for the year ending September, 1941, the turnover had risen to about $680,000. It is not permissible to state in detail how this phenomenal increase has occurred but I can assure your that 80 per cent of this amount represents work which is directly associated with the war-time effort. Perhaps the most amazing feature of our experience in rehabilitation work since the war has been the capacity of the tuberculous patient in rehabilitation centres to become the useful productive agent in the office, factory and field. Nothing has been more exhilarating than to find tuberculous patients defying air raid warnings and sticking to their benches until the final message for shelter is given. Practically no time is now lost from these annoying interruptions and the records show that the contribution of rehabilitation centres to the national effort in the prosecution of the war is not negligible.

Closely linked up with tuberculosis administration has been the evacuation of general hospitals, complete with staff and students, to the country, to the newly built hospitals under the Ministry of Health. Had it been suggested in peace-time that the union of a general hospital and a sanatorium should take place under any circumstances, the idea would have been flouted in so many quarters that its possibility would never have materialized. Now, however, it is no unusual thing to find the general hospital cheek by jowl with the sanatorium; with the medical staff intermingling and assisting each other to the extent that

tuberculosis becomes, as in fact it always is, an integral part of general medicine. Those of us who have spent a life-time in tuberculosis work have also come to appreciate at close quarters the standpoint of the general surgeon and physician and these latter have from the same close quarters learned much of tuberculosis that they had forgotten. This experience is perhaps one of the most outstanding of the war and it is impossible to say how far the lessons which are being learned will be put into practice in post-war years. Quite clearly it has been to the advantage of large numbers of medical students to have bed-side teaching on clinical tuberculosis in all its forms and to understand more of the specialized methods in treatment which they could never see or experience in general hospitals in large cities. Since the Battle of Britain, tuberculosis work in this country has made valiant efforts in reorganization and not without considerable success. That we have had our difficulties is clear and at the time of writing we have far surmounted one of the greatest, namely, the adequate staffing of our institutions. The calls made upon male staff for the services and upon female staff, including nurses, for the factories, military, hospitals and other national organizations have made administration in sanatoria a nightmare to many medical superintendents. It is even on record that certain sanatoria have had to close down certain blocks of beds on account of the shortage of nursing and domestic staff. There is no order to compel either nurses or domestic servants to work in sanatoria and I regard personally this situation as one of the most serious with which we are faced in tuberculosis work in this country at present. Salaries have been adjusted but still the shortage continues.

In the welter of discussions which have taken place at meetings of tuberculosis experts in this country since the war, two matters are worthy of special record. First comes the strong support that has been forthcoming from practically all organizations on the value of mass radiology in the detection of tuberculous disease. It has taken the war to bring the necessity for mass radiology home to us, for war means the accumulation of large numbers in government service either as soldiers, sailors, airmen or factory workers and the opportunities for the examination of large numbers by one or other of the methods now advocated are enormous. The figures which have been obtained from investigations already made in selected groups do not differ substantially from those that have been reported from similar investigations in the United States of America and the general consensus is that by mass radiological methods we are likely to discover more cases of tuberculosis than by any other means at our command. There is still some division of opinion as to the precise and exact method to be adopted, but there is no division of opinion as to the desirability of the principle. The matter is not one, however, which is confined to the realm of medical investigation for it has its repercussions in the social and economic life of the country and especially in the future welfare of those who may be detected as suffering from the disease in a clinically recognizable form. The old dictum that "it does not pay a patient to be diagnosed in an early stage" will have to be combated by some system of State allowances which will safeguard the individual and his dependents if he is to be given the full benefits which early diagnosis

ensures. The very simplicity of the method is important but there is a strong feeling that, if mass radiology is to be completely successful and is to be acceptable to the large majority of the population, it should form part of a general medical examination and should not be thrust upon a public with the word tuberculosis as the only excuse for its adoption. A most praiseworthy effort has recently been made by the National Association for the Prevention of Tuberculosis in declaring its policy on this very matter and by urging on government departments, industrial concerns and others the desirability of mass radiology in the detection of symptomless tuberculosis. The second important event which is happening in this country and is largely the outcome of the war is the attempt to bring more coördination into the activities of the three great voluntary tuberculosis organizations in this country. This is very largely a matter of domestic policy but many of us in this country look upon the American Tuberculosis Association as an ideal which might be followed in principle if not in detail in this country. The National Association for the Prevention of Tuberculosis in England has a record of over forty years of magnificant work especially in tuberculosis propaganda. The Joint Tuberculosis Council is a collection of experts from various societies and forms a solid block of authoritative opinion on every aspect of tuberculosis reasearch, while the Tuberculosis Association is essentially a clinical body which has been responsible for papers and discussions on every aspect of clinical tuberculosis. The degree of overlapping, however, has been so marked in recent years that strong efforts are now being made to obtain more unification in procedure by some form of coördination.

Viewing the position as a whole since the beginning of the war, we can take some consolation in the fact that we have done our best in the face of odds which at one time appeared overwhelming. In certain directions perhaps we have made progress and it certainly looks as if some of the lessons we have learned in these two and a half eventful years will bear fruit in the post-war years. Nevertheless these cold, calculating figures which are presented to us from time to time from the Registrar General's Offices and Government departments tell us something of the real facts and prove to us all that our efforts in war must be multiplied many times over if we are to prevent tuberculosis becoming the evil scourge that it can be if left for even a short period without being attacked from every possible angle. The number of deaths from tuberculosis in males for the second quarter of 1940–1941 was nearly 600 more than for the similar quarter of 1938–1939; the increase in females was over 400 for the same periods. There has been a proportionately greater increase from other forms of tuberculosis, the bulk of which was caused by tuberculous meningitis—one of the surest indications of uncontrolled mass infection. This is no doubt evidence of one of the penalties we are paying for war and in this country we are facing this position with experience of another war which taught us similar lessons. There is always the possibility that it may require a soaring of tuberculosis morbidity and mortality rates to bring the real significance of the disease to the minds of politicians and public alike, so that public enactment may enable us to undertake all the methods for prevention, diagnosis and treatment which we know can limit the spread of the

disease and ultimately reduce the number of deaths from it. In another connection I have said something which may be fitting for the conclusion of this brief summary of the position of tuberculosis in England to-day—"All the evidence shows that we have a very long way to go before we are in a position to eradicate foci of massive infection in the homes of many thousands of people, and until public opinion enables tuberculosis workers in all parts of the world to investigate by clinical, radiological, statistical and any other means at our disposal the nests of infection which are impeding the fall in the death rate and maintaining the morbidity rate from tuberculosis, we are never likely to obtain the results we desire and which our enthusiasm deserves."

ARYTENOID EXTRUSION WITH ROENTGENOLOGICAL STUDIES[1]

WILLIAM C. VOORSANGER[2]

One sees very little in the literature regarding the extrusion or sloughing off of any bony substance connected with the larynx, such as an arytenoid or cricoid. Chevalier Jackson states (*Diseases of the Larynx*, Saunders Publishing Co., 1937): "Extrusion of the laryngeal cartilages may follow necrosis of these cartilages in typhoid fever, syphilis and tuberculous perichondritis." He considers the perichondritis of tuberculosis as an osteomyelitis of the involved area complicated by the presence of secondary invading organisms. The cricoid cartilage is more frequently involved than the arytenoids. Following the ulceration of the mucosa the perichondrium becomes elevated, polymorphonuclear leucocytes infiltrate the tissue and necrosis of the cartilagebegins. The prognosis of cartilaginous necrosis is generally good depending upon adequate drainage. Eliason and Stevens (Am. J. Surg., 1941, *51*, 387) are of the opinion that the type of tissue reaction in tuberculous perichondritis depends upon the degree of tissue resistance to the tubercle bacillus. They believe that an exudative lesion occurs when tissue resistance is low and a productive lesion, such as the development of fibrotic tuberculomata or papillomata, when tissue resistance is high. These authors mention the reports of both Eschweiler and Randrath who found miliary tubercles in calcified laryngeal cartilages following haematogenous infection, giving support to the view that tuberculous chondritis may be intrinsic in origin in some cases.

In perichondritis of the arytenoid or cricoid cartilages there is frequently immobility of the arytenoid cartilages due to involvement of the cricoarytenoid joint. External palpation of the larynx usually discloses absence of the usual clean-cut laryngeal contours. X-ray studies may show changes from the normal contour of the laryngeal cartilages and the extent of the oedema. The complications of tuberculous perichondritis include abscess, necrosis of the cartilage, extrusion of the sequestrum, atresia of the laryngeal lumen and chondroma. While the prognosis of the cartilaginous necrosis is often good the subsequent stenosis presents a more unfavorable outlook. Whether the necrotic cartilage is extruded or not, the absence of the normal structural resistance for the maintenance of the laryngeal lumen results in a permanent atresia.

This condition must happen quite often, since in tuberculosis of the larynx, particularly in its advanced stage, there must be considerable sloughing of parts. The report of the following case is therefore of extreme interest because all of us interested in its study, which continued over a period of months, believe that for the first time we have been able to demonstrate by tomographic pictures of the larynx that one arytenoid is absent.

[1] Presented at the meeting of the California State Tuberculosis Association at Los Angeles, April 2, 1942.

[2] 490 Post Street, San Francisco, California.

Case Report

B. C., aged forty, married, male, native of California, occupation, salesman. This patient gave a history of having been treated for pulmonary tuberculosis by Dr. George B. Miller of San Francisco. His pulmonary condition became arrested following artificial pneumothorax on the left and he continued his occupation, that is, the maintaining of a small dairy lunch at Sunnyvale.

About April 1, 1941, he was taken to the San Jose Hospital for the removal of the left tuberculous testicle. While there he noticed that he was having difficulty in swallowing and in breathing. He was taken home and for about four days continued to have great difficulty in swallowing and in breathing. He was brought to the California Sanatorium on April 9, 1941, where examination showed a man breathing in stridor. He was cyanotic. He had lost twenty pounds in the course of a week, due to his inability to swallow. His pulse was 160 and his condition such that death seemed imminent. Dr. W. H. Murphy, laryngologist of San Mateo, was called immediately and a tracheotomy was deemed absolutely necessary.

Before the tracheotomy, examination of the larynx showed the cords to be in good condition with no evidence of tuberculous laryngitis. In back of the left arytenoid one could see a reddish mass about the size of a small walnut. The impression at this time was that this was either a calcified lymph node or a tuberculoma. Immediately after the tracheotomy the patient was definitely relieved and could breath normally. For several weeks after the operation he seemed to thrive but he could not swallow solids, and stated that "they would not go down." There was considerable pain on the left side of the throat, just above the tracheotomy wound. One day after a severe coughing spell he coughed up a mass about the size of the end of a man's thumb. This contained hard, elongated particles, which on microscopical examination proved to be bone. The pathological examination was done by Dr. G. Y. Rusk. After the expectoration of this mass the patient was able to swallow all kinds of food and was able to breath comfortably when his tracheotomy tube had been plugged for five hours. An X-ray picture showed a tumor mass on the left side of the trachea above the tracheotomy tube with an elongated calcified particle in the centre of it. The origin of this mass was given much consideration. It could be a foreign body, causing an inflammatory area, it could be a tumor or it could be a cyst.

In August a bronchoscopic examination was made and a portion of the mass extracted. The pathological report stated that it was not malignant. Since September 12, 1941, the patient has been carefully observed by Drs. Wallace Smith and Lewis F. Morrison, laryngologists, whose examination showed that the right vocal cord was absolutely fixed, that there was considerable swelling (probably oedema) to one side of the right arytenoid, and that the left side of the larynx was clear. They have recommended that the tracheotomy tube be left in place.

In order to determine the origin of the mass and the cause of the right vocal cord fixation, numerous tomographic pictures of the larynx were made (see figures 1 to 4). The consensus of the chest men, laryngologists, bronchoscopists and roentgenologists interested in this matter was that this condition was a "sloughed" arytenoid due to tuberculosis of the larynx. The patient is under constant observation, although he is working full time. He feels perfectly well, weighs 172 pounds, speaks in a normal voice and can breath comfortably with the tracheotomy tube plugged for twenty-four hours.

It is something more than a year since the original tracheotomy was performed on this man. Under the date of March 12, 1942, Dr. Lewis F. Morrison, in describing the right arytenoid, makes the following statement: "I do not feel that this diminution in size is due solely to the paralysis nor to any optical illusion that might occur due to the fact that the opposite side is active and on attempted phonation does tend to override the smaller right side. Even when

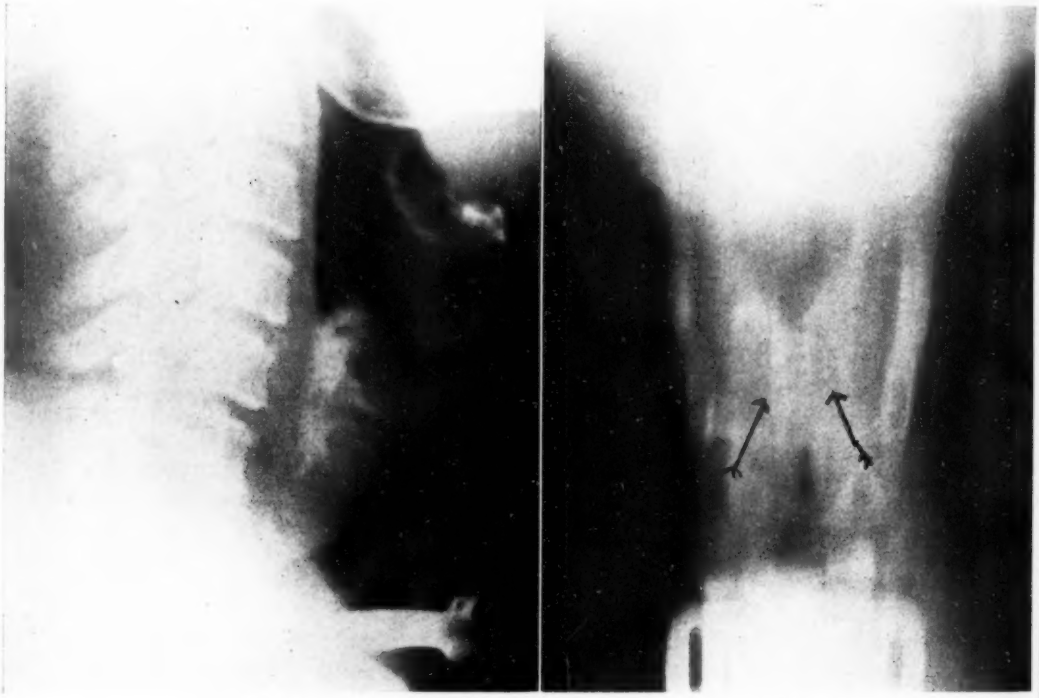


FIG. 1 FIG. 2

FIG. 1. Lateral view of laryngeal calcification.

FIG. 2. Antero-posterior tomograms of the larynx show well defined calcification in the laryngeal cartilages. The difference in calcification in the right and left side is demonstrable but the interpretation in the A-P plane tomogram (figure 1), as compared with the oblique planes (figures 3 and 4), is more difficult and probably less accurate for the small structural changes occurring in lesions of the larynx. The technique in the oblique tomograms is as simple as the antero-posterior position.

this does happen, the level of the surfaces of the right and left vocal cords are on an equal plane. There is a definite absence of substance of the right arytenoid."

At the present writing the patient is perfectly well, weighs 180 pounds, is working full time. The right vocal cord is ankylosed, but all ulceration has completely healed. The larynx is gradually taking on a different appearance. The right arytenoid area is less than half the size of its mate. This applies to height, width and thickness. The general contour is not that of a normal arytenoid. The mesial surface and the *processus vocalis* appear more nearly

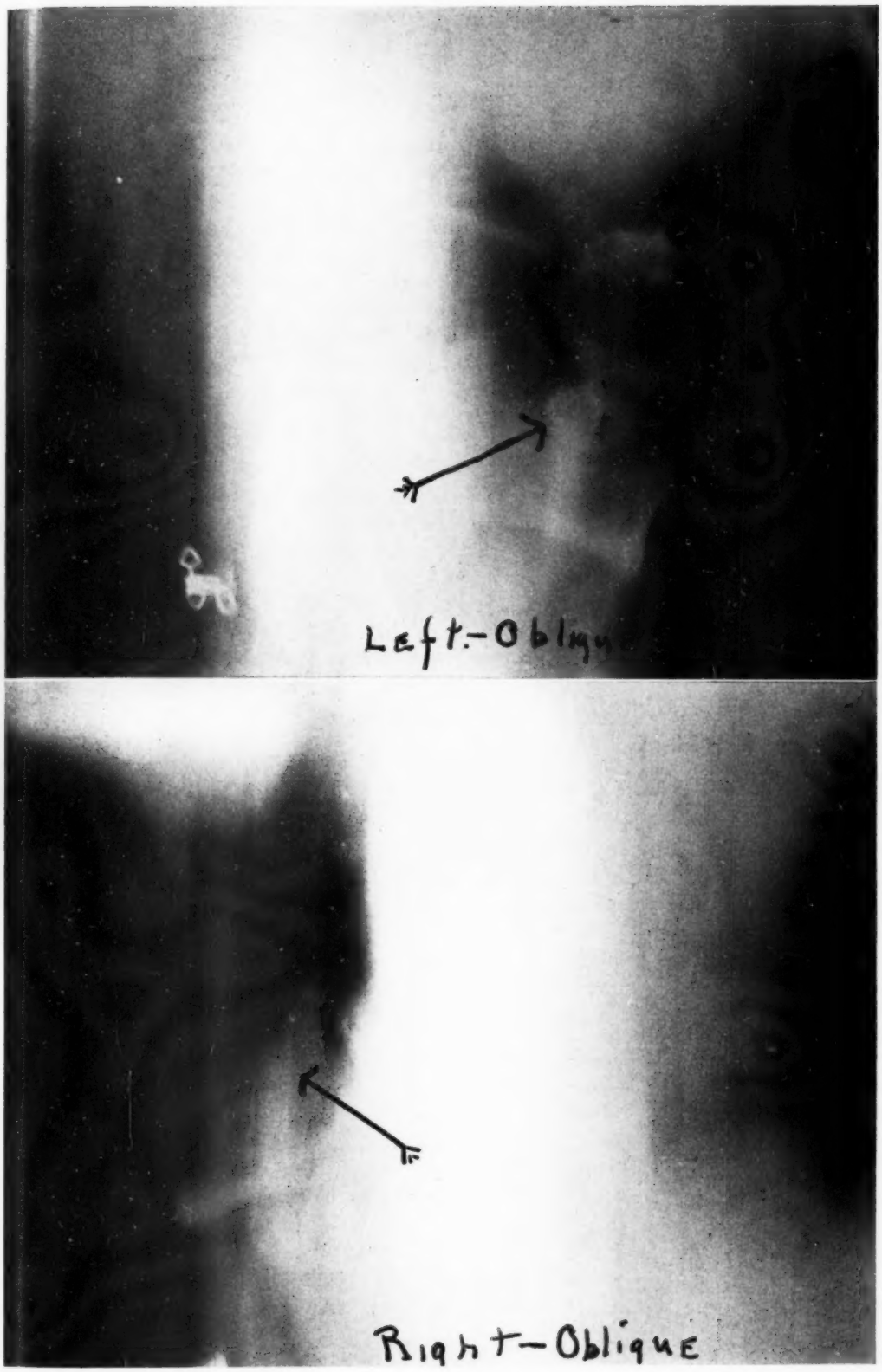


FIG. 3. (Upper) Oblique tomogram of the left side of the larynx. The calcified arytenoid is marked with an arrow and the fine detail in this plane is shown by comparison with the A-P tomograms in figure 1.

FIG. 4. (Lower) Oblique tomogram of the right side of the larynx; the absence of the arytenoid is demonstrable. Compare with figure 3.

normal than any other portion. This patient still carries his tracheotomy tube and seems to have no distress whatever in swallowing or breathing and speaks in a normal tone of voice.

The absence of this arytenoid could only have been proven by a series of tomographic pictures, which as far as we know has never been attempted previously in a laryngeal condition of this nature. It demonstrated beyond the shadow of a doubt that the right arytenoid was missing and that therefore the expectorated mass which contained bone was calcified arytenoid. It is of considerable interest that this patient's tuberculosis of the larynx did not advance but healed and that his physical condition is so good that he can continue his occupation uninterruptedly.

SUMMARY

A patient with healed tuberculosis of the left lung after two years of pneumothorax treatment was operated for the removal of a tuberculous left testicle. While convalescing from this operation he acquired a painful throat and difficulty in swallowing with severe coughing attacks. After four days his respiration was completely obstructed. He was brought to the sanatorium breathing in stridor. A life-saving tracheotomy was performed. The patient progressed very well but could not swallow solids. After two months he expectorated a mass about the size of the end of a thumb, the contents of which upon pathological examination proved to be bony structure. This mass, which had been observed by roentgenological examination prior to tracheotomy, was at first thought to be a tuberculoma. Being a bony structure this diagnosis did not hold and we were presented with the problem of deciding what sort of a bony mass could be extruded from the larynx. A series of tomographic X-ray pictures proved the contents of the mass to be an extruded right arytenoid. We believe that this is the first time tomographic X-ray pictures have been used in this manner to demonstrate laryngeal disease.

SUMARIO

A un enfermo con una tuberculosis curada del pulmón izquierdo tras dos años de tratamiento con neumotórax, se le operó para extirparle el testículo izquierdo, también tuberculoso. Mientras convalecía de la operación, el enfermo manifestó angina y disfagia con graves ataques de tos. A los cuatro días la respiración estaba completamente obstruída. Llevado al sanatorio el enfermo, con un estridor respiratorio, se le ejecutó una traqueotomía para salvarle la vida. La reposición marchó muy bien, pero el enfermo no podía ingerir sólidos. A los dos meses esputó una pieza como del tamaño del extremo de un dedo pulgar, cuyo contenido resultó ser tejido óseo al ser examinado patológicamente. Al principio se había creído que esa masa, que había sido observada roentgenológicamente antes de la traqueotomía, era un tuberculoma. Por tratarse de un tejido óseo hubo que descartar el diagnóstico y quedó en pie el problema de decidir qué clase de tumefacción ósea podía ser expulsada de la laringe. Una serie de roent-

genografías tomográficas demostró que el contenido de la masa era un aretinoides derecho. Parece que ésta es la primera vez que se haya empleado la tomografía en esta forma para demostrar la existencia de laringopatía.

The following have participated in the preparation and observation of this case: Drs. William C. Voorsanger; W. H. Murphy; James Conant of the California Sanatorium (bronchoscopic work and study of literature); Harry Graham, bronchoscopic work; Wallace Smith and Lewis F. Morrison, treatment and observation; F. H. Rodenbaugh and Alexander Petrilli, roentgenology; G. Y. Rusk, pathology.

BROWNING'S METEOROPATHOLOGICAL OBSERVATIONS IN TUBERCULOSIS[1]

WILLIAM F. PETERSEN

About ten years ago Dr. Charles Browning of Los Angeles, aware of my interest in meteoropathology, placed at my disposal data that had been collected in the tuberculosis wards of the Los Angeles County Hospital during the years 1910–1913. The actual observations and records were made by Mr. E. J. Ellsworth under Doctor Browning's supervision. This material had been carefully studied and a summary was prepared by Doctor Browning. From the manuscript I shall later quote pertinent paragraphs.[2]

In view of the fact that an appreciation of the rôle of meteorological factors, as they may be related to tuberculosis symptomatology, is apparently gaining ground in medical thought after an interval of more than half a century, I thought that a publication of some of Browning's material might be of interest.

I do not consider it within the range of this brief record to discuss the meteorological environment at length, other than to call attention to the fact that the weather in the Los Angeles region presents a number of unusual features, predicated on local topography. The proximity of the Pacific Ocean and its fogs provides a wider range of effective temperatures for the population than would be indicated by the official temperature records; the nearness of the great desert toward the southeast provides a region from which hot, dry, low pressure air masses not infrequently pass over the Los Angeles region (Santa Ana winds). The coast range itself, arising abruptly at the rear, serves, too, in deflecting air masses and causing peculiar local weather conditions.

By comparison with the region of the storm tracks, the meteorological environment is relatively tranquil and the energy demand on the human organism is less (1), but abrupt changes in the meteorological environment, to which the human must accommodate, do occur. The effective diurnal range of temperature may be very great, the chilling effects of the fogs, the dehydrating effect of the desert winds as well as their peculiar irritation (in part due to particulate matter held in suspension) may all be of significance for the normal, and of exaggerated importance for the much more sensitive individual who has a tuberculous infection.

As all these varying environmental forces which we include in microclimate need find no mention in the official meteorological record, so, too, it must be kept in mind that we cannot, from a mere symptomatic record of the patient, always estimate the effectiveness of the weather on the patient. Browning recognized this: "Again, the subjective conditions recorded of patients are to a

[1] From the Department of Pathology, Bacteriology and Public Health, University of Illinois College of Medicine, Chicago, Illinois.

[2] Browning reported a study of the *Effect of Climatic Conditions on Important Symptoms in Tuberculosis* at the annual meeting of the American Climatological Association in 1908, later published in the November number of the Southern California Practitioner for 1908.

limited degree indices of the actual conditions of the patients, and many equally important conditions appear to observers and patients which are less easily recorded, and which do not bear a constant relation to the symptoms most prominently shown on the charts." For instance, Browning describes illustrative meteorological situations as well as their effect on the attitude of the tuberculous patients observed on the wards: "*Combination Number One.* The barometer is gradually rising, the humidity slowly falling. This will nearly always give us the wind west of north, the velocity at normal or above, a clear or clearing day and more or less sunshine. The effect of this combination is remarkable. I find the patients pleasant, and in some cases jovial, inclined to be optimistic as to the future; in fact, looking on their surroundings with a degree of contentment."

"*Combination Number Two.* The barometer is falling either gradually or rapidly, the humidity is rising and becoming more oppressive as the hours go by; these conditions usually give us a wind from the east or north with a velocity below normal, a foggy or cloudy day with little or no sunshine. The effect on the patients of this combination is entirely different from the one first mentioned, in that they are pessimistic, cross, very irritable, some of them unreasonable in their demands. It is true that there are many other combinations in climatic conditions; sometimes they are composites of the first and second but usually conditions are those mentioned above."

"A *third combination* is noticeable occasionally during the winter, and results in the 'Northers,' characterized by an abnormally rapid rise in barometric pressure. The sky is clear, relative humidity falls, the wind is northeast, north or northwest. This condition is accompanied by a marked drying of the mucous membrane, causing great discomfort in some and comfort in others. There is a generally increased nervous tension which is exceedingly disagreeable to those most susceptible, and an agreeable amount of stimulation in the phlegmatic. These nervous phenomena are quite noticeable even in the lower animals."

These comments were written when our air mass analysis had not yet developed to its present extent. Nevertheless Doctor Browning and Mr. Ellsworth clearly differentiated the effect of differences in the response of the tuberculous patient not only in general terms but *specifically of the effect of the different air masses* on the pathological processes.

Browning and Ellsworth prepared a series of graphs illustrating the association of change in the clinical symptomatology with the meteorological environment. I have selected but two of the series which illustrate their findings. The first for the period of September and October, 1912 (figure 1) and the second for April, 1913 (figure 2).

In figure 1 deaths have been indicated by black squares immediately over the date line, haemorrhages by the X sign. In the graph barometric pressure, maximal and minimal daily temperatures, and maximum humidity are indicated.

The graph has been subdivided into five portions **(A)**, **(B)**, **(C)**, **(D)**, and **(E)**, and of these periods **(B)** and **(D)** represent phases when there was a distinct increase in environmental temperature. In connection therewith it will be noted that 8 deaths occur during the period **(A)**. With **(B)** there were no deaths,

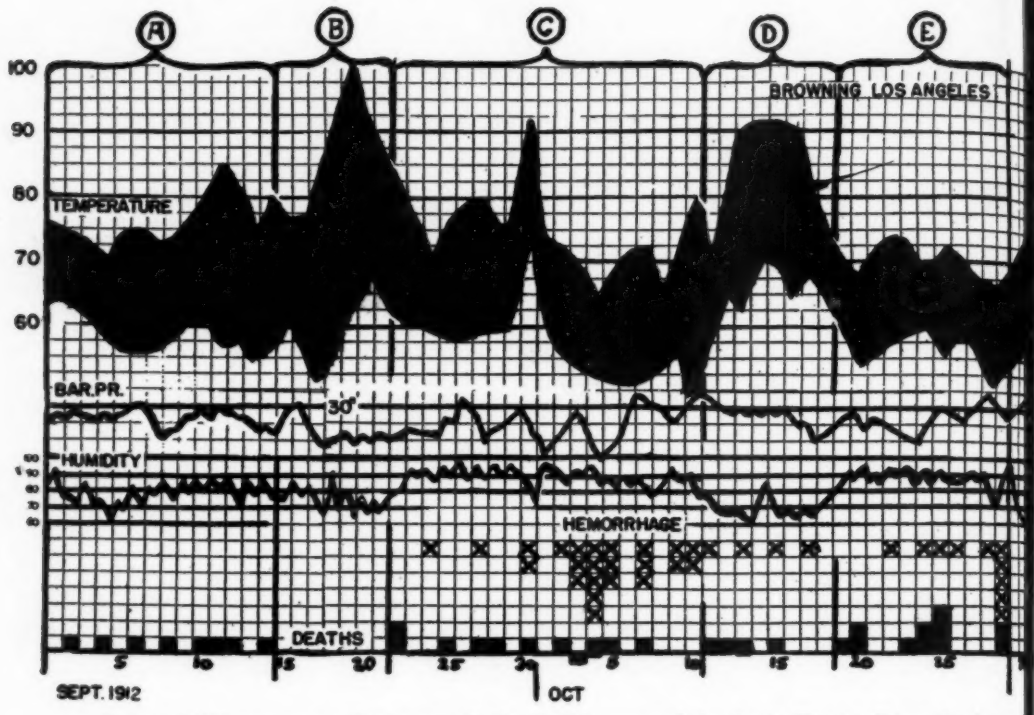


FIG. 1. Meteorogram to illustrate the haemorrhages and deaths in Doctor Browning's cases for September and October, 1912.

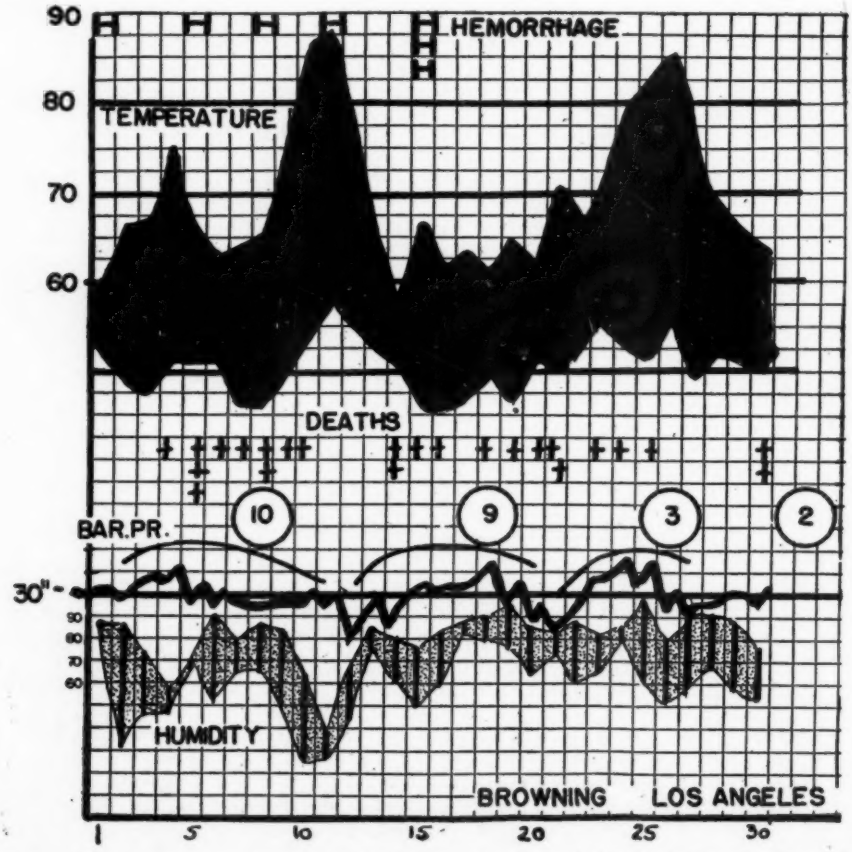


FIG. 2. Meteorogram to illustrate the haemorrhages and deaths in Doctor Browning's cases for April, 1913.

then 10 deaths occur with the period **(C)**, 4 with the period **(D)** and 11 with period **(E)**. Haemorrhages appear in a cluster early in October and many were again precipitated on October 29. In general it was apparent that death was less frequent with periods of rising temperature, while haemorrhages occur during periods of declining temperature. Naturally, haemorrhage as well as death can occur at any time but in general, haemorrhage occurs in the tuberculous individual with a sudden increase in blood pressure, and such pressor episodes are commonly associated with environmental situations which entail peripheral vasoconstriction. But haemorrhage may also occur with a phase of metabolic fatigue most often following in the wake of a period of cold (all accentuated by the passage of subsequent warmer air masses) and with this there is greater digestion of tissue (and fibrin), the venous pressure is apt to increase, and bleeding may result. The accentuation at either pole will depend not only on the individual meteorological episode, but on the season.

In the graph for the month of April, 1913, haemorrhages are indicated by the capital letter H, deaths by small crosses. In this graph maximal and minimal temperature is indicated by the black field.

Here 4 death "episodes" can be determined. With the first, beginning with the increase in barometric pressure evident between the 4th and 5th of October, there were 10 deaths. During the second and third episodes, beginning about the 13th of the month, there were 9 and 3 deaths respectively. Then a final phase of colder weather was associated with 2 deaths on the 30th of the month. Three haemorrhages were precipitated with the sharp decline in environmental temperature that reached a crest on the 15th of the month.

BROWNING'S CONCLUSIONS

Browning and Ellsworth observed that the period of the equinox is more difficult for the tuberculosis patient living in the Los Angeles area; it is an observation that goes back to Hippocrates. The greater variability of the spring merely accentuates the relative acidotic organic phase and there is a lowering of tissue tone, accelerated digestion at the focus, activation, and with this haemorrhage or intoxication; the autumnal variability increases the load on the heart at a time when the relative alkalosis may accentuate vascular and connective tissue resistance because of a sharp increase in tone. This, too, may be too great a strain.

The rôle of variation of the environment *per se* is extremely important. If autonomic disturbances initiated by environmental forces exceed the possibility of proper restoration of equilibrium, the patient will be injured under all circumstances. This feature of environmental variability carries with it an inherent danger even in a relatively tranquil region, such as that of Los Angeles.

In the analysis of the effectiveness of the weather change on patients, Browning wrote that: "*climatic conditions can only act to a certain extent as determining factors in producing symptoms recorded, and climatic conditions are always a complex system, certain phenomena of which may be used as indices, these indices varying in degree of prominence with varying complexity.*" In other words, he

definitely recognized that it was the complex air mass, not an individual index, that was of significance.

Second, he observed that the greater the variability, that is, the suddenness and frequency of weather change, the more pronounced the clinical effect and, furthermore, that greater variability was apt to occur from the 15th of March to the first of April and from the middle of September to the 5th of October in the Los Angeles region, that is, in the spring and in the autumn. With long continued weather of high temperatures and humidity and low barometric pressure, the trend to pleural pain and haemorrhage might be increased, as well as the number of deaths. Finally, he observed that the frequency of death was increased from one to six in the morning and from five to eleven in the evening.

These clinical observations of Browning and Ellsworth are of interest because they are clear leads to the underlying pathophysiological changes that condition the patient.

Because of the diurnal rhythm, a relative sympathicotonia obtains in the early morning hours and a relative vagotonia begins to overbalance in the afternoon and reaches a crest sometime in the evening before midnight.

Death in tuberculosis occurs most often: (*1*) with sudden increase in arterial and arteriolar tone which throws a sudden burden on a deficient heart muscle or may cause haemorrhage or accentuate a peripheral anoxia (chill) with the resulting production of deleterious products of anoxic metabolism; or (*2*) with loss of vascular tone and with dilatation of the vascular bed. The blood flow to the right heart is then decreased, venous engorgement occurs, the heart muscle is poorly supplied and cardiac collapse follows.

Thus periods of *undue increase* or *undue decrease* of vascular tone will jeopardize the patient. In the diurnal physiological cycle, such periods are apt to occur in the morning hours or in the evening, when Browning and Ellsworth observed greater mortality.

The effect of opposite types of weather will affect different patients in varying degrees. Weather that tends to increase tone increases resistance in some individuals but may cause death in others (2). On the other hand, if the increase in tone is too abrupt or continued too long, products of anoxia flood the organism, there is a loss of vascular tone to a point far below that previously observed in the patient, with this there is increased hydration, accentuation of tissue digestion about the tuberculous lesion, etc.

Such a phase may be induced by prolonged periods of unduly high temperature and humidity and low barometric pressure, such as those observed by Browning and Ellsworth. Here again their clinical observations are in line with what we may anticipate from the purely physiological concept.

Bogen (3) of Los Angeles later published a study that confirmed the observations of Browning. His study brought sharply into focus the marked " 'periodicity' of pulmonary haemorrhage in tuberculosis, and suggests that there may be extrinsic factors rather than mere chance to explain the marked irregularity in the incidence of this phenomenon."

He came to the conclusion, as the result of the analysis of temperature, humid-

ity and wind velocity, "that for each of these aspects of the weather there are optimum conditions under which the least number of haemorrhages may be expected to occur, but that marked variations from this optimum in any one of them, particularly in the direction of excessive heat or humidity or absence of wind, are apt to be associated with an increase in the incidence of haemoptyses."

Perhaps Bogen's statistical demonstration "that the incidence of pulmonary haemorrhage goes hand in hand with the height of barometric pressure is the most definite and unambiguous finding in this investigation" is most striking confirmation of Browning's thesis. Bogen observed that, with diminished barometric pressure, the blood pressure was low and vice versa. He found it "highly probable that the effect of meteorological conditions on the frequency of haemoptysis may be found to act through this mechanism."

It is not my purpose to discuss the many relevant observations that have appeared in the literature in recent times. Some of these studies present very elaborate analyses of a whole variety of factors that are of significance in the environment of the tuberculous patient, but practically all are in agreement that a most potent factor and one that is universally effective resides in the condition of the air mass in which the patient happens to exist. It is obvious, of course, that each particular geographic region will present individual problems of adjustment for the tuberculous patient, but if the close integration of the pathophysiology with the meteorology is appreciated, some of the puzzling clinical expressions of the disease will be more readily clarified.

To one such study I shall briefly refer, namely, that of Schuberth and Gruner (4), representing as it does the collaboration of the clinician and the physicist of the Physical Meteorological Observatory at Davos in Switzerland. This presents a statistical analysis of the integration of the day by day symptoms of large groups of tuberculous patients with the rather complicated meteorological changes that were observed for more than a year (1931–1933) at Davos. The studies amply confirm the Browning thesis (5).

After noting the greater sensitivity of the tuberculous patient to meteorological alterations, Schuberth and Gruner call attention to the fact that the symptomatology elicited will vary with the disposition of the subject: "certain types of air masses do not necessarily always elicit the same response but there is no doubt that certain types of air mass change initiate comparable symptoms in the group at large. The effect of the frontal passage is the more pronounced the greater the interval between like fronts but also the greater the extremes in divergence from the preceding front."

CONCLUSION

Attention is directed to the early recognition by Browning of Los Angeles that the effectiveness of the meteorological environment of the tuberculous patient resided in both frequency and amplitude of change. While he studied in considerable detail individual indices of weather change, his clear-cut finding that we deal with air mass change rather than with individually measured factors (temperature, barometric pressure, humidity, etc.) deserves recognition because the observation was made at a time when air mass analysis was in its infancy.

CONCLUSIONES

Llámase la atención sobre el reconocimiento temprano por Browning, de Los Angeles, de que la eficacia del ambiente meteorológico del tuberculoso radica tanto en la frecuencia como en la amplitud de los cambios. Aunque dicho autor estudió bastante a fondo los índices individuales de las alteraciones meteorológicas, merece reconocimiento su hallazgo bien definido de que se trata de alteraciones de la masa aérea más bien que de factores medidos individualmente (temperatura, presión barométrica, humedad, etc.), porque esa observación fué realizada en una época en que los análisis de la masa aérea se encontraban todavía en su infancia.

REFERENCES

(1) Petersen, W. F., and Milliken, M. E.: The Patient and the Weather, Volume I, Part 2, Autonomic Integration, Chapter II, Edwards Brothers, Ann Arbor, Michigan, 1936.
(2) Petersen, W. F., and Milliken, M. E.: Ibid., Volume IV, Part 2, Organic Disease, 1937, page 663, Tuberculosis Subject #3.
(3) Bogen, Emil: Pulmonary hemorrhage, California & West. Med., 1930, *33*, 1.
(4) Schuberth, A., and Gruner, R.: Über Wettereinflüsse auf Tuberkulosekranke, Ztschr. f. Tuberk., 1939, *83*, 12.
(5) Browning, Charles C.: The effect of climatic conditions on important symptoms in tuberculosis, South. California Practitioner, November, 1908.

STATISTICAL DATA

Edited by MARY DEMPSEY

DECLINE IN TUBERCULOSIS DEATH RATE CONTINUES

Provisional figures reported by state departments of health indicate that in the United States the 1941 death rate per 100,000 population from tuberculosis, all forms, was 44.4, compared with 45.9 in 1940. This preliminary rate for 1941, which is subject to minor revision, is the lowest mortality rate on record for this country, though the decline in recent years has been rather slight.

Migration, incident to the war and to the accompanying increase in industrial activity, has made it difficult, if not impossible, to ascertain what population changes have occurred in the various states during the past year or two. Moreover, the United States Bureau of the Census has not yet published estimated population figures since the census was taken on April 1, 1940. The death rates shown for each state have been based on the estimated population as of July 1, 1941, using the arithmetical method for estimating these figures. In view of these unavoidable circumstances it is quite possible that the death rates listed may be subject to somewhat greater correction than has formerly been the case.

Although the mortality rate of 44.4 per 100,000 population for continental United States will undoubtedly prove to be very nearly accurate, those states with a large influx of population since early 1940 are listed with too high death rates for the reason that their population estimates are too low. Conversely, in states with few war activities the death rates are too low because many of their residents have left for industrial centers or for service with the armed forces.

Six western states have recorded death rates below 20 per 100,000 population; these states, 4 of which are sparsely settled, include among their residents no large racial group peculiarly susceptible to tuberculosis. In addition, it is probable that the mortality in all these states is somewhat understated because of recent migration to industrial communities.

Arizona with its large number of health seekers and its numerous Indians still has by far the highest tuberculosis mortality among the states. Four other states and the District of Columbia have death rates above 65 per 100,000 population. (See table 1.)

The American Public Health Association in its appraisal of health activities has established a standard with reference to the reporting of new cases of tuberculosis. In order to meet this standard two new cases should be reported per annual death. The record of case reporting in this country indicates that the standard is slowly but gradually being met.

In 1930 reported new cases of tuberculosis numbered 1.43 per death in that year. Eleven years later in 1941 this ratio had increased to 1.80. (See table 2.)

It is quite possible that the figures on reported new cases for all these years should be discounted slightly because of duplications. In other words, the case which is diagnosed in Pennsylvania should, in accordance with the law, be re-

TABLE 1

New cases reported, deaths and death rates from tuberculosis, by states

(Provisional figures as reported by state departments of health)

1941

STATE	NEW CASES REPORTED	NUMBER OF DEATHS (RECORDED)	NEW CASES REPORTED PER DEATH	DEATH RATE PER 100,000 POPULATION
United States	106,413	59,173	1.80	44.4
Alabama	2,809	1,473	1.91	51.4
Arizona	1,257*	864	1.45	171.2
Arkansas	925†	965	0.96	48.9
California	7,525	3,743	2.01	53.6
Colorado	1,622	524	3.10	46.1
Connecticut	1,325	578	2.29	33.4
Delaware	179	152	1.18	56.5
District of Columbia	1,986	577	3.44	77.9
Florida	981	916	1.07	47.7
Georgia	2,635	1,385	1.90	43.8
Idaho	103	84	1.23	15.8
Illinois	9,412	3,470	2.71	43.4
Indiana	1,348	1,293	1.04	37.3
Iowa	552	390	1.42	15.2
Kansas	829	408	2.03	22.4
Kentucky	1,748	1,928	0.91	67.0
Louisiana	2,009	1,316	1.53	55.0
Maine	490	250	1.96	29.2
Maryland	3,018*	1,366	2.21	74.2
Massachusetts	3,282	1,632	2.01	37.4
Michigan	5,371	1,723	3.12	32.4
Minnesota	1,871	751	2.49	26.6
Mississippi	1,445	1,016	1.42	46.0
Missouri	2,379	1,729	1.38	45.2
Montana	466	201	2.32	35.5
Nebraska	186	204	0.91	15.3
Nevada	80	59	1.36	52.7
New Hampshire	238	104†	2.29	20.9
New Jersey	3,559	1,850	1.92	44.0
New Mexico	910*	351	2.59	65.2
New York	15,165	6,208	2.44	45.5
North Carolina	2,300	1,769	1.30	49.0
North Dakota	502	117	4.29	18.0
Ohio	5,297	2,929	1.81	41.9
Oklahoma	1,522	1,062	1.43	44.9
Oregon	571‡	297†	1.92	26.9
Pennsylvania	4,944	4,048	1.22	40.4

* Special effort is made to obtain the number of new cases reported exclusive of "primary" or "childhood type" cases which in some states are reportable. All figures in this column are exclusive of "primary" or "childhood type" cases except those carrying this footnote.

† 1940 figure; 1941 not yet obtained.

‡ Estimated.

TABLE 1—*Continued*

STATE	NEW CASES REPORTED	NUMBER OF DEATHS (RECORDED)	NEW CASES REPORTED PER DEATH	DEATH RATE PER 100,000 POPULATION
Rhode Island	579	269	2.15	37.3
South Carolina	701	853‡	0.82	44.4
South Dakota	239	175	1.37	26.9
Tennessee	3,607	2,332	1.55	79.0
Texas	2,840	3,694	0.77	56.9
Utah	159*	62	2.56	11.1
Vermont	110	125	0.88	34.4
Virginia	2,704§	1,638	1.81§	60.5
Washington	1,777	657¶	2.70	37.4
West Virginia	1,686†	823	2.05	42.8
Wisconsin	1,092	779	1.40	24.5
Wyoming	78	34	2.29	13.4
Hawaii	622	259	2.40	60.2
Puerto Rico	8,565	4,648	1.84	243.4

* Special effort is made to obtain the number of new cases reported exclusive of "primary" or "childhood type" cases which in some states are reportable. All figures in this column are exclusive of "primary" or "childhood type" cases except those carrying this footnote.

† 1940 figure; 1941 not yet obtained.

‡ Estimated.

§ Cases shown are for pulmonary tuberculosis only. Cases per death based on 1,495 deaths from pulmonary tuberculosis.

¶ Corrected for residence.

TABLE 2

New cases of tuberculosis reported, deaths† from tuberculosis, and ratio of reported cases per death: United States, 1930–1941*

YEAR	NEW CASES* REPORTED	DEATHS† FROM TUBERCULOSIS	REPORTED NEW CASES PER DEATH
1941	106,413‡	59,173‡	1.80‡
1940	103,268	60,428	1.71
1939	101,470	61,609	1.65
1938	107,021	63,735	1.68
1937	112,394	69,324	1.62
1936	107,086	71,527	1.50
1935	111,856	70,080	1.60
1934	113,020§	71,609	1.58
1933	114,412§	74,842	1.53
1932	121,961	78,390	1.56
1931	124,858	84,679	1.47
1930	124,940	87,509	1.43

* Reported by state departments of health.

† Census figures for 1933–1940, inclusive; census figure plus Texas State Health Department figures for 1930–1932, inclusive.

‡ Provisional figures reported by state departments of health.

§ Cases for North Dakota omitted because not available.

ported in that state. Subsequently the patient may go to Arizona for treatment where the same case is presumably reported again. Since the migration of tuberculous patients has shown a tendency to decline in recent years, it is probable that the 1930 ratio of reported cases per death should be discounted more than that in 1941. Thus, we have some reason to believe that the actual improvement in case reporting throughout the country during the past ten or twelve years is in reality somewhat greater than the census figures indicate.

AMERICAN TRUDEAU SOCIETY

Report of the Committee on Educational Literature

Dr. J. Emerson Dailey, *Chairman*
Dr. Frank L. Jennings Dr. E. S. Mariette Dr. James C. Walsh

At the last meeting of the Society, the above members were appointed for the Committee on Educational Literature (1941–1942).

As stated by the Executive Committee of the Society at its meeting in New York City, December 6, 1940, "It is the function of the Committee on Educational Literature to act in an advisory capacity to the Health Education Service of the National Tuberculosis Association, to review copy and manuscripts for literature, publications and motion pictures issued by the National Tuberculosis Association for distribution to the general public, giving special attention to the medical facts presented. Monographs produced on request by recognized experts on special subjects may be submitted to the Committee for comment, but the final material shall be the responsibility of the author."

Material for examination and comment is sent by the Central Office of the National Tuberculosis Association to each member of the Committee. After examination of this material each member addresses his comments to the Chairman and at the same time sends copies of his remarks to each of the other members. Further exchange of comments may be made. The Chairman finally abstracts the remarks and suggestions and informs the Central Office of the final report of the Committee.

A number of different items were reviewed by the Committee during this past year consisting of manuscripts for motion pictures, manuals and booklets and drafts of pamphlets, leaflets and posters.

Some examples of the above items are as follows:

1: All of the material for the 1942 E.D.C., composed of forty-one pages of drafts, of pamphlets and leaflets.
2: A working manual for volunteers on conducting a campaign, twenty pages.
3: A twelve-page manuscript of a pamphlet for the general practitioner.
4: A leaflet for Negro education.
5: A fourteen-page pamphlet, "Why Does Tuberculosis Run in Families?"
6: A sixteen-page manuscript on tuberculosis published by the Metropolitan Life Insurance Company.
7: Ideas, platform suggestions and blueprint for the 1943 E.D.C.
8: Scenario for a movie setting forth the tuberculosis situation as affected by the present war.

At the invitation of the National Tuberculosis Association one of the members of this Committee, Dr. E. S. Mariette, attended the meeting of the Advisory Committee on Health Education of the National Conference of Tuberculosis Secretaries and the Health Education Service of the National Tuberculosis Association held in New York City, January 13, 1942, to plan the Early Diagnosis

Campaign for 1943 and other activities having to do with health education. This representation served admirably in keeping this Committee in touch with health education plans and possibly contributed valuable suggestions to the discussions.

RECOMMENDATION

In past years medical consultants appointed by the Executive Committee of the National Tuberculosis Association usually sat in with the Advisory Committee on Health Education. These medical consultants were not reappointed after the creation of this Committee on Health Education of the American Trudeau Society which may, therefore, be interpreted as taking the place of the former medical consultants. Therefore, it is recommended that this Committee as a whole, or a representative of it, be authorized to attend the Annual Conference of the Advisory Committee on Health Education.

AMERICAN TRUDEAU SOCIETY

Report of the Membership Committee

Dr. Hugh B. Campbell, *Chairman*
Dr. C. M. Sharp Dr. John B. Barnwell

The activities of the Membership Committee of the previous year have been continued by your present Committee diligently and in a manner befitting the type of organization we represent.

Much of the credit for the success we have had in this year is due to the fine cooperation, advice and support we have had from Mrs. Elizabeth Stoltenkamp, Dr. Cameron St. C. Guild, Mr. L. E. Lascelle and Mrs. Henrietta Reilly of the Central Office.

In an endeavor to attract physicians who might desire to join the Society because of an interest in tuberculosis, various methods of approach were attempted.

A: Members were requested to either send names of interested physicians to the Central Office or to discuss the matter with the individual either in conversation or by letter.
B: The directory of the American Medical Association was checked for tuberculosis specialists.
C: The files of the National Tuberculosis Association, the Pneumothorax Directory and the subscription list of the American Review of Tuberculosis were carefully combed.
D: The Committee did not confine its activities to the United States, but also sought members in Canada and Latin America.

We have been pleased by the response obtained from members of the American College of Physicians. In November, a list of 235 physicians, known to be members of this organization, were approached by letter. Up until the present time, 63 of this number have submitted their applications. Of their total membership reported in 1941, 550 are now members of the American Trudeau Society. The New York Office is, at the present time, mailing a promotional letter to a number of those in the groups mentioned above who have not as yet sought membership. It is our belief that about 100 will be obtained as a result of this activity.

The Membership Committee reports to you that the membership of the American Trudeau Society, on March 31, 1942 was 1,400, as compared with a membership of 828 on March 31, 1941, an increase of 581 during the year. A possible field for further expansion of membership still exists in the South, Southwest and Northwest.

The Committee has given considerable time and study to the desirability of a membership certificate for the members of the American Trudeau Society. There has been a general desire on the part of the membership that such a certificate be issued. As a result of the study, the Committee unanimously recommended to the Council on November 5, 1941, that a membership certificate be issued to each member of the Society. This certificate should simply state, "That the individual has been elected a member of the American Trudeau

Society, the Medical Section of the National Tuberculosis Association, on—— date." We assume action will be taken on this matter at the next annual meeting.

The Committee also considered the advisability of revising the blanks used for securing membership data. It was suggested that the application form should limit the number of activities in which the applicant might be interested. Doctor Barnwell has suggested that the applicant eliminate entirely the special societies to which he belongs, as that information is contained already in the American Medical Association Directory and need not be duplicated by us.

The activities of this Committee have been carried on entirely by correspondence. As Chairman, I desire to express my thanks to the other members of the Committee for their coöperation and support.

AMERICAN TRUDEAU SOCIETY

Report of the Committee on Constitutional Revision

Dr. Benjamin L. Brock, *Chairman*
Dr. Ezra Bridge Dr. Carl R. Howson

The Committee on Constitutional Revision has been active throughout the past year. The members of the Committee have depended almost entirely on correspondence through the mails in expressing our thoughts to one another regarding the revisions which were first submitted to the Executive Committee in December and now to the membership for their action in Philadelphia. The Committee was fortunate in having Doctor Bridge spend one morning at the executive office where many detailed revisions were discussed and made.

Many of the proposed changes in the Constitution have been minor, but some have been of major importance and, at the same time, controversial. Much letter writing has been necessary between us and the executive office to iron out many of these problems. The final draft is in Doctor Guild's hands, and we submit it to you and the membership with the sincere hope that the proposed changes may, for the time being at least, satisfy the heads of our changing and growing Society. We welcome any proposals from the membership at the Philadelphia meeting.

Needless to say, it has been more than a pleasure to have served as a member of this Committee during the past year. I wish to acknowledge the unusual willingness and desire on the part of Doctor Bridge and Doctor Howson to lend themselves frequently and unselfishly to this task. They have, indeed, been the mainstays in revising this Constitution for submission to the members.

INDEX OF SUBJECTS AND AUTHORS

Abscess, pulmonary, putrid, Acute, 121
Acute putrid pulmonary abscess, 121
Adolescents, healthy, Gastric lavage in, 622
Age characteristics of tubercles, 329
ALEXANDER, JOHN. Treatment of post-operative pulmonary complications, From the point of view of the surgeon, 664
Ambulatory pneumothorax, 67, 639
AMERICAN TRUDEAU SOCIETY:
Report of the Committee on Industrial Tuberculosis, 213
Report of the Committee on Coexistent Syphilis and Tuberculosis, 361
Report of the Committee on Coöperation with the American Board of Internal Medicine, 362
Report of the Committee on Undergraduate Medical Education, 468
Report of the Committee on X-ray Apparatus and Technique, 469
Report of the Committee on Tuberculosis Sanatorium Standards, 584
Report of the Committee on Rehabilitation, 586
Report of the Committee on Educational Literature, 701
Report of the Membership Committee, 703
Report of the Committee on Constitutional Revision, 705
Anaemia of tuberculous patients following thoracoplasty, 27
Animal inoculation, Atypical findings on, 625
Animals, infecting, by inhalation, Device for, 205
ARONSON, JOSEPH D., AND SAYLOR, ROBERT M. A portable X-ray unit for field studies in tuberculosis, 352
Arytenoid extrusion with roentgenological studies, 684
Atelectasis, pulmonary, Bronchial obstruction and, 524
Atypical findings on animal inoculation, 625
AUFSES, ARTHUR H. Treatment of war wounds of the thorax, 111

Bacilli, tubercle, Initial tissue response to, 319
——, ——, Media for, 560
Bacilli, tubercle, staining, New method of, 199
——, ——, Survival of, in books, 549
BARACH, ALVAN L., MOLOMUT, NORMAN, AND SOROKA, MAX. Inhalation of nebulized promin in experimental tuberculosis, 268
B-complex deficiency in tuberculosis, 285
BEHN, BORGHILD, AND HASTINGS, D. R. Pneumothorax cases treated at a clinic, 656
BERKE, RUDOLPH, AND SANDLER, BENJAMIN P. Treatment of tuberculosis with a low carbohydrate diet, 238
Bilateral pneumothorax, Spontaneous, 105
BLAISDELL, J. L., AND HAMBLETON, A. A device for infecting animals by inhalation, 205
Bone tuberculosis, children with, Tuberculin sensitivity in, 532
BONILLA, J. L., JR. Pleurisy with effusion, 59
BOOKS:
ADAMS, F. DENNETTE. Cabot and Adams physical diagnosis, 466
ALEXANDER, HARRY L. Synopsis of allergy, 466
AMBERSON, J. BURNS, JR. Chest X-ray interpretation, 455
CARVALLO, CONSTANTINO J. Memoria que Presenta al Congreso Nacional el Ministro de Salud Publica, Trabajo y Prevision Social, 466
CHADWICK, HENRY D., AND POPE, ALTON S. The modern attack on tuberculosis, 456
ESPINOZA GALARZA, MAX. Colapso pulmonar quirúrgico, 466
FONSO GANDOLFO, CARLOS, AND RUGIERO, HUMBERTO R. Tuberculosis pulmonar, 455
HODGES, LEIGH MITCHELL. The people against tuberculosis, 460
HUEPER, W. C. Occupational tumors and allied diseases, 466
ITURBE, P., DELGADO RIVAS, H., AND SOTO MATOS, R. Investigacion sistematica de la tuberculosis en zonas urbanas, rurales, semi-rurales, industriales petroleras e indigenas en el estado zulia, 466

JACKSON, CHEVALIER, AND JACKSON, CHEVALIER L. Diseases and injuries of the larynx, 467
KILDUFFE, ROBERT A., AND DE BAKEY, MICHAEL. The blood bank and the technique and therapeutics of transfusions, 464
LEWIS, JULIAN HERMAN. The biology of the Negro, 461
MENENDEZ, FRANCISCO J., AND HERNANDEZ GONZALO, PEDRO. Le tuberculosis traqueobronquial, 467
NYSWANDER, DOROTHY B. Solving school health problems, 467
SCHIFF, FRITZ, AND BOYD, WILLIAM C. Blood grouping technic, 465
SHERWOOD, NOBLE PIERCE. Immunology, second edition, 462
SKLÁDAL, J. The pleuro-subpleural zone, 467
URQUIJO, CARLOS A., AND WAISSMANN, MARIO. El raquitismo en el hijo de tuberculosa, 467
VON ROSEN, ERIK. Studien über die Lungendurchleuchtung in der Tuberkulosebekämpfung, 467
WILSON, NETTA W., AND WEISMAN, S. A. Modern medicine, Its progress and opportunities, 463
Anuario de Epidemiologia y Estadistica Vital Ano 1940, 467
Chronic pulmonary disease in South Wales coalminers, 457
Directory of Medical Specialists, Certified by American Boards, 1942, 467
Memoria del Primer Congreso Venesolano de la Tuberculosis, Caracas, December 8 to 11, 1938, 467
Tuberculosis Hospital and Sanatorium Directory, 466
Tuberculosis in industry. Report of the Symposium held at the Saranac Laboratory for the Study of Tuberculosis, Saranac Lake, New York, June 9–14, 1941, 459
War medicine, 467
Books, Survival of tubercle bacilli in, 549
BRAVERMAN, MORRIS M. Anaemia of tuberculous patients following thoracoplasty, 27
Bromsulphalein liver function test in pulmonary tuberculosis, 439
Bronchi, trachea, and lungs, Haemorrhage from the, of nontuberculous origin, 126
Bronchial obstruction and pulmonary atelectasis, 524
Browning's meteoropathological observations in tuberculosis, 690

Cadmium sulphide, Treatment of pulmonary tuberculosis by, 139
Carbohydrate diet, low, Treatment of tuberculosis with a, 238
Carcinoma of the oesophagus, Tuberculosis in a, 346
CARR, DAVID T., AND SPAIN, DAVID, M. Tuberculosis in a carcinoma of the oesophagus, 346
Case-finding demonstration, Tuberculosis, in San José, Costa Rica, 179
Catheter drainage of tuberculous cavities, Hastings on, 546
Cavities, tuberculous, catheter drainage of, Hastings on, 546
Chemotherapy of tuberculosis, 277
——— ——— ———, Method for studies in, 101
Children with bone tuberculosis, Tuberculin sensitivity in, 532
CHODOFF, R. J., AND SAVACOOL, J. W. Plasma prothrombin in tuberculous patients, 432
Chronic pulmonary tuberculosis, 505
CIOCCO, ANTONIO, AND WOLFF, GEORG. Infection, social environment and heredity in tuberculosis, 142
CLARK, C., AND CORPER, H. J. Congenital tuberculin hypersensitiveness and specific tuberculo-allergic immunity, 309
CLARK, LAWRENCE T., AND FOLLIN, STEPHEN F. Quantitative standardization of tuberculin purified protein derivative, 77
CLERF, LOUIS H. Treatment of postoperative pulmonary complications, From the point of view of the bronchoscopist, 675
Clinic, Pneumothorax cases treated at a, 656
Clinical episode in tuberculosis and the meteorological environment, 407
COHN, MAURICE L., AND CORPER, H. J. Media for tubercle bacilli, 560
College students, Tuberculosis in, 227
COLWELL, CHARLOTTE A. See GUNN, F. D., *et al.*, 612

Complications, pulmonary, postoperative, Treatment of,
From the point of view of the surgeon, 664
From the point of view of the internist, 666
From the point of view of the pathologist, 674
From the point of view of the bronchoscopist, 675
From the point of view of the nurse, 676
Congenital tuberculin hypersensitiveness and specific tuberculo-allergic immunity, 309
CONN, RAYMOND W. Effect of pregnancy upon tuberculin reaction, 350
CONROY, ELIZABETH. See HOLLON, HARRIETT, *et al.*, 568
Contralateral pneumothorax, 72
CORPER, H. J., AND CLARK, C. Congenital tuberculin hypersensitiveness and specific tuberculo-allergic immunity, 309
——, ——. ——., —— COHN, MAURICE L. Media for tubercle bacilli, 560
Costa Rica, San José, Tuberculosis case-finding demonstration in, 179

Deficiency, B-complex, in tuberculosis, 285
DIAMOND, SIDNEY, AND JACKSON, CHEVALIER L. Haemorrhage from the trachea, bronchi and lungs of non-tuberculous origin, 126
Diet, low carbohydrate, Treatment of tuberculosis with a, 238
Dog, Experimental pulmonary tuberculosis in the, BCG immunization, 612
DORMER, B. A., WILES, F. J., AND FRIEDLANDER, J. Treatment of pulmonary tuberculosis by cadmium sulphide, 139
Drainage, catheter, of tuberculous cavities, Hastings on, 546
DUCA, CHARLES J., AND STEINBACH, M. MAXIM. Experimental tuberculosis in hyperglycaemic albino rats, 304

EDITORIAL. The patient with occasionally positive sputum following apparently adequate treatment, 582
EDWARDS, HERBERT R. Experience with mass X-ray equipment, 472
Effect of pregnancy upon experimental tuberculosis in rabbits, 93
—— —— —— —— tuberculin reaction, 350
Effusion, Pleurisy with, 59
Elderly persons, Undiagnosed pulmonary tuberculosis in, 164
Electrocardiogram in pulmonary tuberculosis, 35
Electron microscope, Studies of mycobacteria with the, 587
ELLIOTT, JABEZ H. Hastings on catheter drainage of tuberculous cavities, 546
ENGLAND, N. J. See STOBIE, W., *et al.*, 1
England, Tuberculosis in, during war, 677
Environment, meteorological, Clinical episode in tuberculosis and the, 407
——, social, Infection, and heredity in tuberculosis, 142
Enzymes as factors in resistance to tuberculosis, 600
Experimental pulmonary tuberculosis in the dog, BCG immunization, 612
—— tuberculosis in hyperglycaemic albino rats, 304
—— —— —— rabbits, Effect of pregnancy upon, 93
—— ——, Inhalation of nebulized promin in, 268
—— ——, Promin in, 187
Exposed populations, Tuberculosis in, 172
Extrapleural pneumothorax, 646
Extrusion, Arytenoid, with roentgenological studies, 684

FEINSTONE, W. HARRY. A method for studies in chemotherapy of tuberculosis, 101
FELDMAN, WILLIAM H., MANN, FRANK C., AND HINSHAW, H. CORWIN. Promin in experimental tuberculosis, 187
Fenestration of the first thoracic ribs, 574
FLOYD, C., NOVACK, H. A., AND PAGE, C. G. Gastric lavage in healthy adolescents, 622
FOLLIN, STEPHEN F., AND CLARK, LAWRENCE T. Quantitative standardization of tuberculin purified protein derivative, 77
Foreign-body granulomata, Tubercles and, 295
FRANCO, S. E., AND GUREVITCH, J. Atypical findings on animal inoculation, 625
FRIEDLANDER, J. See DORMER, B. A., *et al.*, 139
FULLAM, ERNEST F. See ROSENBLATT, MILTON B., *et al.*, 587

Function test, liver, Bromsulphalein, in pulmonary tuberculosis, 439
Fungi, pathogenic, Isolation and identification of, from sputum, 365

Gastric lavage in healthy adolescents, 622
GEARY, PAUL. Extrapleural pneumothorax, 646
GERBER, ISADORE E., AND KRUGER, ALFRED L. Bromsulphalein liver function test in pulmonary tuberculosis, 439
GERSTL, BRUNO, AND TENNANT, ROBERT. Enzymes as factors in resistance to tuberculosis, 600
GESSLER, ALBERT E. See ROSENBLATT, MILTON B., *et al.*, 587
GLASS, W. H. B-complex deficiency in tuberculosis, 285
GOLDBURGH, HAROLD L., AND URBACH, ERICH. Haemorrhagic-necrotic reaction to tuberculin PPD, 418
Granulomata, foreign-body, Tubercles and, 295
GUGGENHEIM, ALBERT, ROTENBERG, LOUIS, AND LAFF, HERMAN I. Tuberculosis of the oesophagus, 577
Guinea pig inoculation for tuberculosis, Silicon dioxide in, 568
GUNN, F. D., SHEEHY, J. J., COLWELL, CHARLOTTE A., AND MILLS, M. A. Experimental pulmonary tuberculosis in the dog,
BCG immunization, 612
GUREVITCH, J., AND FRANCO, S. E. Atypical findings on animal inoculation, 625

Haemograms, Interpretation of, in pulmonary tuberculosis, 1
Haemorrhage from the trachea, bronchi and lungs of nontuberculous origin, 126
Haemorrhagic-necrotic reaction to tuberculin PPD, 418
HAMBLETON, A., AND BLAISDELL, J. L. A device for infecting animals by inhalation, 205
HASTINGS, D. R., AND BEHN, BORGHILD. Pneumothorax cases treated at a clinic, 656
Hastings on catheter drainage of tuberculous cavities, 546
HENDERSON, BEATRICE, AND MILLER, RAYMOND E. Undiagnosed pulmonary tuberculosis in elderly persons, 164
Heredity, Infection, social environment and, in tuberculosis, 142
HINSHAW, H. CORWIN. See FELDMAN, WILLIAM H., *et al.*, 187
HOLLON, HARRIETT, SPRICK, MARIAN, CONROY, ELIZABETH, AND WILSON, ELIZABETH. Silicon dioxide in guinea pig inoculation for tuberculosis, 568
HOWARD, PHILIP J., JOHNSTON, JOSEPH A., AND MITCHELL, C. LESLIE. Tuberculin sensitivity in children with bone tuberculosis, 532
HYMAN, HAROLD THOMAS. See ZUCKER, GARY, *et al.*, 277
Hyperglycaemic albino rats, Experimental tuberculosis in, 304
Hypersensitiveness, tuberculin, Congenital, and specific tuberculo-allergic immunity, 309

Identification, Isolation and, of pathogenic fungi from sputum, 365
Immunity, tuberculo-allergic, specific, Congenital tuberculin hypersensitiveness and, 309
Infecting animals by inhalation, Device for, 205
Infection, social environment and heredity in tuberculosis, 142
Inhalation, infecting animals by, Device for, 205
of nebulized promin in experimental tuberculosis, 268
Initial tissue response to tubercle bacilli, 319
Inoculation, animal, Atypical findings on, 625
——, guinea pig, for tuberculosis, Silicon dioxide in, 568
Inspection of the lungs during respiration, 109
Interpretation of haemograms in pulmonary tuberculosis, 1
Isolation and identification of pathogenic fungi from sputum, 365

JACKSON, CHEVALIER L., AND DIAMOND SIDNEY. Haemorrhage from the trachea, bronchi and lungs of nontuberculous origin, 126
JAFFIN, ABRAHAM E. See KRUGER, ALFRED L., *et al.*, 50
JOHNSTON, JOSEPH A. See HOWARD, PHILIP J., *et al.*, 532

JONES, EDNA M., RAFFERTY, T. N., AND WILLIS, H. S. Primary tuberculosis, 392

KELLOGG, DOUGLAS S., AND LINSMAN, JOSEPH F. Fenestration of the first thoracic ribs, 574
KELLY, RUBY G. See WOODRUFF, C. E., *et al.*, 319
KENT, EDWARD M. Bronchial obstruction and pulmonary atelectasis, 524
KRUGER, ALFRED L., AND GERBER, ISADORE E. Bromsulphalein liver function test in pulmonary tuberculosis, 439
——, —— ——., POTTER, BENJAMIN P., AND JAFFIN, ABRAHAM E. Management of the minimal tuberculous lesion, 50
KURUNG, JOSEPH M. The isolation and identification of pathogenic fungi from sputum, 365
——, ——, AND YEGIAN, DIRAN. Response of scar tissue to tuberculin, 196

LAFF, HERMAN I. See GUGGENHEIM, ALBERT, *et al.*, 577
LEAMING, MARY A. See WOODRUFF, C. E., *et al.*, 319
LICHTENSTEIN, M. R. Tuberculin reaction in tuberculosis during pregnancy, 89
LINSMAN, JOSEPH F., AND KELLOGG, DOUGLAS S. Fenestration of the first thoracic ribs, 574
Liver function test, Bromsulphalein, in pulmonary tuberculosis, 439
LUCACER, M. Contralateral pneumothorax, 72
Lungs, Inspection of the, during respiration, 109
——, trachea, bronchi and, Haemorrhage from the, of nontuberculous origin, 126
LYGHT, CHARLES EVERARD. Tuberculosis in college students, 227

Management of patients with occasionally positive sputum after apparently adequate therapy,
  Clinical aspects, 475
  Pathological aspects, 479
  Nursing aspects, 481
  Public health aspects, 483
—— —— the minimal tuberculous lesion, 50
MANN, FRANK C. See FELDMAN, WILLIAM H., *et al.*, 187
MANNING, ALICE LOVE. Treatment of postoperative pulmonary complications, From the point of view of the nurse, 676
MARCUS, HENRIETTE, AND SCHWARTZ, SIDNEY P. The electrocardiogram in pulmonary tuberculosis, 35
MARIETTE, E. S. An improved steam suction apparatus, 355
MARK, HILBERT. Tuberculosis in exposed populations, 172
Mass X-ray equipment, Experience with, 472
McDOUGALL, J. B. Tuberculosis in England during war, 677
McMENEMEY, W. H. See STOBIE, W., *et al.*, 1
McNETT, ESTA H. Management of patients with occasionally positive sputum after apparently adequate therapy, Nursing aspects, 481
Media for tubercle bacilli, 560
Medical aspects of the rehabilitation of the tuberculous, 489
Meteorological environment, Clinical episode in tuberculosis and the, 407
Meteoropathological observations, Browning's, in tuberculosis, 690
Method for studies in chemotherapy of tuberculosis, 101
Microscope, electron, Studies of mycobacteria with the, 587
MILLER, RAYMOND E., AND HENDERSON, BEATRICE. Undiagnosed pulmonary tuberculosis in elderly persons, 164
MILLS, M. A. See GUNN, F. D., *et al.*, 612
Minimal tuberculous lesion, Management of the, 50
MITCHELL, C. LESLIE. See HOWARD, PHILIP J., *et al.*, 532
MOLOMUT, NORMAN. See BARACH, ALVAN L., *et al.*, 268
MORRISS, W. H. Pneumothorax treatment, 628
Mycobacteria, Studies of, with the electron microscope, 587

NAYER, H. R., AND PINNER, MAX. Chronic pulmonary tuberculosis, 505
Nebulized promin, Inhalation of, in experimental tuberculosis, 268
NEUHOF, HAROLD, AND TOUROFF, ARTHUR S. W. Acute putrid pulmonary abscess, 121

Nontuberculous origin, Haemorrhage from the trachea, bronchi and lungs of, 126
NOVACK, H. A. See FLOYD, C., *et al.*, 622

OBITUARY: Peters, LeRoy S., 1882–1941, 358
Observations, meteoropathological, Browning's, in tuberculosis, 690
Obstruction, Bronchial, and pulmonary atelectasis, 524
Oesophagus, carcinoma of the, Tuberculosis in a, 346
——, Tuberculosis of the, 577
Operations, phrenic nerve, Results of, 262
OPPENHEIMER, H. E., AND SPECTOR, H. I. Ambulatory pneumothorax, 67
OWENS, PAUL L. Results of phrenic nerve operations, 262

PAGE, C. G. See FLOYD, C., *et al.*, 622
PAGEL, WALTER. Tubercles and foreign-body granulomata, 295
Pathogenic fungi, Isolation and identification of, from sputum, 365
Patient with occasionally positive sputum following apparently adequate treatment, (editorial), 582
Patients, tuberculous, Plasma prothrombin in, 432
—— with occasionally positive sputum after apparently adequate therapy, Management of,
Clinical aspects, 475
Pathological aspects, 479
Nursing aspects, 481
Public health aspects, 483
Peters, LeRoy S., 1882–1941, in memoriam, 358
PETERSEN, WILLIAM F. Browning's meteoropathological observations in tuberculosis, 690
——, ——. The clinical episode in tuberculosis and the meteorological environment, 407
Phrenic nerve operations, Results of, 262
PINNER, MAX. The patient with occasionally positive sputum following apparently adequate treatment, (editorial) 582
——, ——. Treatment of postoperative pulmonary complications, From the point of view of the pathologist, 674
——, ——, AND NAYER, H. R. Chronic pulmonary tuberculosis, 505
PINNER, MAX. See ZUCKER, GARY, *et al.*, 277
Plasma prothrombin in tuberculous patients, 432
Pleurisy with effusion, 59
Pneumothorax, Ambulatory, 67, 639
——, bilateral, Spontaneous, 105
—— cases treated at a clinic, 656
——, Contralateral, 72
——, Extrapleural, 646
—— treatment, 628
Populations, exposed, Tuberculosis in, 172
Portable X-ray unit for field studies in tuberculosis, 352
Positive sputum, occasionally, Patient with, following apparently adequate treatment, (editorial), 582
—— ——, ——, patients with, after apparently adequate therapy, Management of,
Clinical aspects, 475
Pathological aspects, 479
Nursing aspects, 481
Public health aspects, 483
Postoperative pulmonary complications, Treatment of,
From the point of view of the surgeon, 664
From the point of view of the internist, 666
From the point of view of the pathologist, 674
From the point of view of the bronchoscopist, 675
From the point of view of the nurse, 676
POTTER, BENJAMIN P. See KRUGER, ALFRED L., *et al.*, 50
PPD, tuberculin, Haemorrhagic-necrotic reaction to, 418
Pregnancy, Effect of, upon experimental tuberculosis in rabbits, 93
——, —— ——, —— tuberculin reaction, 350
——, Tuberculin reaction in tuberculosis during, 89
Primary tuberculosis, 392
Promin in experimental tuberculosis, 187
——, nebulized, Inhalation of, in experimental tuberculosis, 268
Protein derivative, purified, tuberculin, Quantitative standardization of, 77
Prothrombin, Plasma, in tuberculous patients, 432
Pulmonary abscess, putrid, Acute, 121

Pulmonary atelectasis, Bronchial obstruction and, 524
—— complications, postoperative, Treatment of,
From the point of view of the surgeon, 664
From the point of view of the internist, 666
From the point of view of the pathologist, 674
From the point of view of the bronchoscopist, 675
From the point of view of the nurse, 676
—— tuberculosis, Bromsulphalein liver function test in, 439
—— ——, Chronic, 505
—— ——, Electrocardiogram in, 35
—— ——, Experimental, in the dog, BCG immunization, 612
—— ——, Interpretation of haemograms in, 1
—— ——, Treatment of, by cadmium sulphide, 139
—— ——, Undiagnosed, in elderly persons, 164
Purified protein derivative, tuberculin, Quantitative standardization of, 77
Putrid pulmonary abscess, Acute, 121

Quantitative standardization of tuberculin purified protein derivative, 77

Rabbits, experimental tuberculosis in, Effect of pregnancy upon, 93
Rafferty, T. N. See Jones, Edna M., *et al.*, 392
Rats, albino, hyperglycaemic, Experimental tuberculosis in, 304
Reaction, Haemorrhagic-necrotic, to tuberculin PPD, 418
——, tuberculin, Effect of pregnancy upon, 350
——, ——, in tuberculosis during pregnancy, 89
Rehabilitation of the tuberculous, Medical aspects of the, 489
Resistance to tuberculosis, Enzymes as factors in, 600
Respiration, Inspection of the lungs during, 109
Response of scar tissue to tuberculin, 196
——, tissue, Initial, to tubercle bacilli, 319
Results of phrenic nerve operations, 262
Ribs, thoracic, first, Fenestration of the, 574
Riggins, H. McLeod. Treatment of postoperative pulmonary complications, From the point of view of the internist, 666
Roentgenological studies, Arytenoid extrusion with, 684
Rosenblatt, Milton B., Fullam, Ernest F., and Gessler, Albert E. Studies of mycobacteria with the electron microscope, 587
Rotenberg, Louis. See Guggenheim, Albert, *et al.*, 577

Sandler, Benjamin P., and Berke, Rudolph. Treatment of tuberculosis with a low carbohydrate diet, 238
Savacool, J. W., and Chodoff, R. J. Plasma prothrombin in tuberculous patients, 432
Saylor, Robert M., and Aronson, Joseph D. A portable X-ray unit for field studies in tuberculosis, 352
Scar tissue, Response of, to tuberculin, 196
Schwartz, Sidney P., and Marcus, Henriette. The electrocardiogram in pulmonary tuberculosis, 35
Sensitivity, Tuberculin, in children with bone tuberculosis, 532
Sheehy, J. J. See Gunn, F. D., *et al.*, 612
Silicon dioxide in guinea pig inoculation for tuberculosis, 568
Siltzbach, Louis E. Medical aspects of the rehabilitation of the tuberculous, 489
Smith, C. Richard. Survival of tubercle bacilli in books, 549
Social environment, Infection, and heredity in tuberculosis, 142
Soderstrom, Kenneth M. Management of patients with occasionally positive sputum after apparently adequate therapy, Public health aspects, 483
Soroka, Max. See Barach, Alvan L., *et al.*, 268
Spain, David M., and Carr, David T. Tuberculosis in a carcinoma of the oesophagus, 346
Spector, H. I., and Oppenheimer, H. E. Ambulatory pneumothorax, 67
Spontaneous bilateral pneumothorax, 105
Sprick, Marian. See Hollon, Harriett, *et al.*, 568

Sputum, occasionally positive, patients with, after apparently adequate therapy, Management of,
Clinical aspects, 475
Pathological aspects, 479
Nursing aspects, 481
Public health aspects, 483
——, pathogenic fungi from, Isolation and identification of, 365
——, positive, occasionally, Patient with, following apparently adequate treatment, (editorial), 582
Staining tubercle bacilli, New method of, 199
Standardization, Quantitative, of tuberculin purified protein derivative, 77
Statistical data, 210, 445, 697
Steam suction apparatus, Improved, 355
STEINBACH, M. MAXIM, AND DUCA, CHARLES J. Experimental tuberculosis in hyperglycaemic albino rats, 304
STOBIE, W., ENGLAND, N. J., AND MCMENEMEY, W. H. The interpretation of haemograms in pulmonary tuberculosis, 1
STOKES, ARTHUR M. Management of patients with occasionally positive sputum after apparently adequate therapy, Clinical aspects, 475
Students, college, Tuberculosis in, 227
Suction apparatus, steam, Improved, 355
Survival of tubercle bacilli in books, 549
SWEANY, HENRY C. Age characteristics of tubercles, 329

TENNANT, ROBERT, AND GERSTL, BRUNO. Enzymes as factors in resistance to tuberculosis, 600
Test, liver function, Bromsulphalein, in pulmonary tuberculosis, 439
THEARLE, WILLIAM H., AND WERNER, WALTER I. Spontaneous bilateral pneumothorax, 105
Therapy, apparently adequate, patients with occasionally positive sputum after, Management of,
Clinical aspects, 475
Pathological aspects, 479
Nursing aspects, 481
Public health aspects, 483
Thoracic ribs, first, Fenestration of the, 574
Thoracoplasty, Anaemia of tuberculous patients following, 27
Thorax, war wounds of the, Treatment of, 111
TICE, FREDERICK. Ambulatory pneumothorax, 639
Tissue response, Initial, to tubercle bacilli, 319
TOUROFF, ARTHUR S. W., AND NEUHOF, HAROLD. Acute putrid pulmonary abscess, 121
Trachea, bronchi and lungs, Haemorrhage from the, of nontuberculous origin, 126
Treatment, apparently adequate, Patient with occasionally positive sputum following, (editorial), 582
—— of postoperative pulmonary complications,
From the point of view of the surgeon, 664
From the point of view of the internist, 666
From the point of view of the pathologist, 674
From the point of view of the bronchoscopist, 675
From the point of view of the nurse, 676
—— —— pulmonary tuberculosis by cadmium sulphide, 139
—— —— tuberculosis with a low carbohydrate diet, 238
—— —— war wounds of the thorax, 111
——, Pneumothorax, 628
Tubercle bacilli, Initial tissue response to, 319
—— ——, Media for, 560
—— ——, staining, New method of, 199
—— ——, Survival of, in books, 549
Tubercles, Age characteristics of, 329
—— and foreign-body granulomata, 295
Tuberculin hypersensitiveness, Congenital, and specific tuberculo-allergic immunity, 309
—— PPD, Haemorrhagic-necrotic reaction to, 418
—— purified protein derivative, Quantitative standardization of, 77
—— reaction, Effect of pregnancy upon, 350
—— —— in tuberculosis during pregnancy, 89
——, Response of scar tissue to, 196
—— sensitivity in children with bone tuberculosis, 532

Tuberculo-allergic immunity, specific, Congenital tuberculin hypersensitiveness and, 309
Tuberculosis, B-complex deficiency in, 285
——, bone, children with, Tuberculin sensitivity in, 532
——, Browning's meteoropathological observations in, 690
—— case-finding demonstration in San José, Costa Rica, 179
——, Chemotherapy of, 277
——, —— ——, Method for studies in, 101
——, Clinical episode in, and the meteorological environment, 407
——, Experimental, in hyperglycaemic albino rats, 304
——, ——, —— rabbits, Effect of pregnancy upon, 93
——, ——, Inhalation of nebulized promin in, 268
——, ——, Promin in, 187
——, field studies in, Portable X-ray unit for, 352
——, guinea pig inoculation for, Silicon dioxide in, 568
—— in a carcinoma of the oesophagus, 346
—— —— college students, 227
—— —— England during war, 677
—— —— exposed populations, 172
——, Infection, social environment and heredity in, 142
—— of the oesophagus, 577
——, Primary, 392
——, pulmonary, Bromsulphalein liver function test in, 439
——, ——, Chronic, 505
——, ——, Electrocardiogram in, 35
——, ——, Experimental, in the dog, BCG immunization, 612
——, ——, Interpretation of haemograms in, 1
——, ——, Treatment of, by cadmium sulphide, 139
——, ——, Undiagnosed, in elderly persons, 164
——, resistance to, Enzymes as factors in, 600
——, Treatent of, with a low carbohydrate diet, 238
——, Tuberculin reaction in, during pregnancy, 89
Tuberculous cavities, catheter drainage of, Hastings on, 546
—— lesion, minimal, Management of the, 50
—— patients, Anaemia of, following thoracoplasty, 27
—— ——, Plasma prothrombin in, 432
——, rehabilitation of the, Medical aspects of the, 489

Undiagnosed pulmonary tuberculosis in elderly persons, 164
URBACH, ERICH, AND GOLDBURGH, HAROLD L. Haemorrhagic-necrotic reaction to tuberculin PPD, 418

VOORSANGER, WILLIAM C. Arytenoid extrusion with roentgenological studies, 684

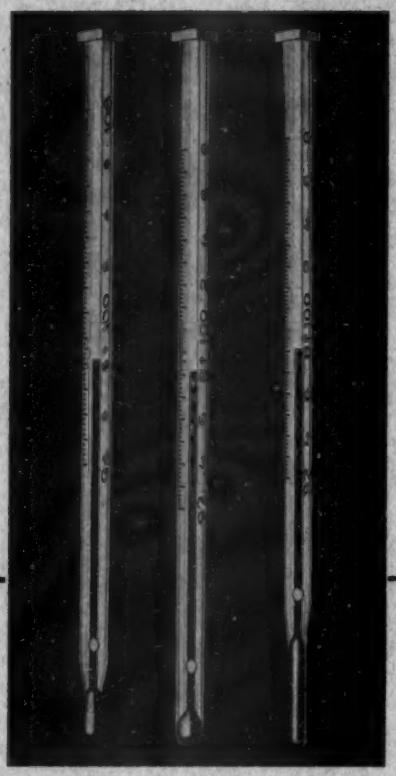
WADE, LEO J. The effect of pregnancy upon experimental tuberculosis in rabbits, 93
War, Tuberculosis in England during, 677
—— wounds of the thorax, Treatment of, 111
WEISS, EMIL. A new method of staining tubercle bacilli, 199
WELLS, C. W. A tuberculosis case-finding demonstration in San José, Costa Rica, 179
WERNER, WALTER I., AND THEARLE, WILLIAM H. Spontaneous bilateral pneumothorax, 105
WILES, F. J. See DORMER, B. A., *et al.*, 139
WILLIS, HENRY STUART. Management of patients with occasionally positive sputum after apparently adequate therapy, Pathological aspects, 479
——, ——. ——. See JONES, EDNA M., *et al.*, 392
WILSON, ELIZABETH. See HOLLON, HARRIETT, *et al.*, 568
WOLFF, GEORG, AND CIOCCO, ANTONIO. Infection, social environment and heredity in tuberculosis, 142
WOODRUFF, C. E., KELLY, RUBY G., AND LEAMING, MARY A. Initial tissue response to tubercle bacilli, 319
Wounds, war, of the thorax, Treatment of, 111

X-ray equipment, mass, Experience with, 472
—— unit, Portable, for field studies in tuberculosis, 352

YEGIAN, DIRAN. Inspection of the lungs during respiration, 109

YEGIAN, DIRAN, AND KURUNG, JOSEPH. Response of scar tissue to tuberculin, 196

ZUCKER, GARY, PINNER, MAX, AND HYMAN, HAROLD THOMAS. Chemotherapy of tuberculosis, 277



Today, as Never Before . . . You Need the *Extra Strength and Dependability* of these "TEMPGLASS" FAICHNEY THERMOMETERS

A wartime economy demands judicious buying of clinical thermometers as well as all other types of sanatorium supplies . . . to help reduce the need for replacements as well as for maximum serviceability.

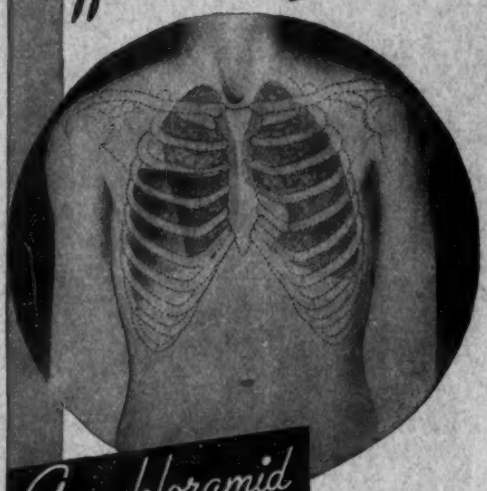
"TEMPGLASS" Thermometers, designed especially for sanatorium use, not only have high resistance to breakage, due to our unique tempering process, but they are also EASIER TO READ because *temperature calibrations are spaced 25% farther apart* than on ordinary clinical thermometers. And every thermometer is "Shake Tested" for quick, easy shake-down.

Prices: *Tempglass, any style bulb:*
per doz . . . $6.50; per gross . . . $72.00

We can still make prompt deliveries. Order today.

FAICHNEY INSTRUMENT CORP.
Watertown, New York

Effective in treating **EMPYEMA**



Azochloramid
N-N'-DICHLORAZODICARBONAMIDINE

Suitable for either irrigation or instillation.

Pronounced stability in the presence of pleural fluid exceeds that of other chlorine germicides.

Reduced frequency of application.

Easily prepared—Economical.

AZOCHLORAMID IS COUNCIL ACCEPTED

SUPPLIED AS:

Azochloramid Saline Mixture for instant preparation of an isotonic solution 1:3300 buffered to pH 7.4.

Now available in a New Economical Hospital Bulk Package. Details on request.

Azochloramid Solution in Triacetin 1:500, an oily solution which is used undiluted.

Azochloramid Solution in Triacetin 1:125 to prepare a solution in Olive Oil 1:2000.

Trial quantities sent to physicians on request.

WALLACE & TIERNAN PRODUCTS, Inc.
Belleville, New Jersey, U. S. A.

a natural source of

THIAMINE
RIBOFLAVIN
NICOTINIC ACID

and other known factors of the
VITAMIN B COMPLEX

MEAD'S BREWERS YEAST TABLETS • Each Mead's Brewers Yeast Tablet contains not less than .06 mg. thiamine (vitamin B_1), .02 mg. riboflavin (vitamin G), and 15 mg. nicotinic acid, together with other factors of the vitamin B complex commonly occurring in brewers' yeast.

MEAD'S BREWERS YEAST POWDER • Each gram (½ teaspoon) supplies not less than .18 mg. thiamine, .06 mg. riboflavin, and .40 mg. nicotinic acid. For infants, Mead's Brewers Yeast Powder can be shaken up in a bottle. For the older child, the product may be shaken up with milk in an ordinary malted milk shaker, with or without cocoa.

Mead's Brewers Yeast is nonviable and is vacuum-packed to prevent oxidation. Packed in brown bottles and sealed cartons for greater protection.

MEAD JOHNSON & COMPANY, EVANSVILLE, INDIANA, U. S. A.